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THE MONTH

The Symposium

IT is a sobering thought that in spite of nigh on fifty years of investigation, we are still lamentably ignorant of the precise role of many of the vitamins in the human body. Fortunately, the manifestations of gross deficiency have been early recognized and dealt with, with the result that conditions such as scurvy, rickets, pellagra and beri-beri are rapidly disappearing from all but the more backward countries of the world. Where the practitioner now runs into difficulty is in trying to assess whether the minor symptoms or signs in his patients are the result of slight degrees of deficiency of one or other vitamin —particularly one of the members of the B-complex. His task has not been made easier by the intensive public advertising campaigns of many of the manufacturers, which have inevitably tended to inculcate into the lay mind the idea that, no matter how balanced the diet, a vitamin supplement is essential for the attainment of health.

An impartial consideration of our symposium this month makes it abundantly clear that, in this country at least, there is seldom any necessity for such supplementation except in the case of infants, children, pregnant and lactating mothers and, in some cases, elderly people living on their own. The symposium as a whole presents a balanced and authoritative review of the subject which should allow the practitioner to assess the present nutritional and pharmacological status of that heterogeneous collection of substances which we still designate as vitamins. Whether, as Dr. Douthwaite suggests in his article (p. 74), the time has come to discard this term altogether, is a matter deserving of careful attention. Now that their chemical nature is known, a term which is scientifically inaccurate might well be allowed to drop out of use. The case for such a move is strengthened by the increasing extent to which these substances are now being used pharmacologically. To place vitamin A, for instance, in the same category as cyanocobalamin is the antithesis of scientific classification.

General Practitioners' Records

IN spite of all the frustrations of the last ten years, it looks as if the general practitioner were coming back into his own. Indeed, it may not be too optimistic to suggest that he may even come to occupy a more important position in the medical hierarchy than ever before. Much, of course, will depend upon the politicians, but just as much will depend upon the extent to which the profession puts first things first. In instilling a right sense of values the College of General Practitioners has played an increasingly

important part since its foundation in 1952. Not the least of its achievements —some would say one of the most important—is the publication by the General Register Office of the first volume of 'Morbidity Statistics from General Practice' (H.M. Stationery Office, price 15*s.* 6*d.*). Two further volumes are projected: one dealing with the distribution of sickness by occupation, and the other with the more clinical implications of general practitioners' morbidity statistics.

The report now published is an analysis of a survey of the records of 106 practices in England and Wales, covering 359,323 National Health Service patients, carried out by the College in conjunction with the General Register Office. Its importance is twofold. It provides convincing evidence that general practitioners are not only able, but willing, to provide records that are capable of statistical analysis. Equally important, it demonstrates that these records are of outstanding value in providing information essential for the accurate assessment of morbidity statistics. Such statistics are of increasing importance for the doctor and the research worker, as well as the administrator. Hitherto, for such statistics we have been dependent upon notifications of infectious diseases, National Health Insurance certificates of incapacity, and hospital records. These obviously do not present a true picture of the incidence of illness. For such a picture the records of general practitioners are necessary. The Grand Old Man of Aysgarth showed how this could be done in the Yorkshire Dales. The College, of which he was the last President, has now shown that what he did for his beloved Dales, the College can do for the nation.

The Englishman's Disease

Bronchitis, particularly chronic bronchitis, has been well named the Englishman's disease. It takes a toll of life and health which is unequalled anywhere else in the world. During the last ten years the crude death rate for bronchitis has never fallen below 559 per million in England and Wales, and in 1957, the latest year for which figures are available, it was 600 per million. Over £7 million a year are paid out of National Insurance funds to claimants with bronchitis in England and Wales, and in 1954 it was responsible for 25,620,000 workdays being lost, compared with the loss of 427,000 days as a result of industrial strikes.

That it is not entirely our climate that can be blamed for this disturbing state of affairs is suggested by the comparable death rates in neighbouring countries: just over 40 per million in the Scandinavian countries, 115 per million in The Netherlands, and 112 in Western Germany. On the other hand, that atmospheric pollution may well be a factor is suggested by the geographical distribution—a point well brought out by the medical officer of health for Salford in his recently published annual report for 1957. This shows that on the average, for the three years 1953-55, the death rate per

million for bronchitis in Salford was 1,372, compared with 480 for Lancashire rural areas. The chronic bronchitic has become such a feature of the medical landscape that there is a tendency to accept him as a permanency. As is noted in the joint report by the General Register Office and the College of General Practitioners on 'Morbidity Statistics from General Practice', bronchitis is the disease most often requiring medical attention. The problem is one that must be tackled, however, on a much larger scale than has hitherto been the case. If, as has been reported, Japan can reduce its death rate from bronchitis from 448 per million in 1947 to 99 in 1955, it seems strange that we have been able to do so little in this country.

The Spectre of V.D.

As reported elsewhere in this issue (p. 140), one of the disturbing features of the annual report of the chief medical officer of the Ministry of Health for 1957 is the 'further steep rise' in the number of new cases of gonorrhœa of both sexes attending venereal disease clinics. In view of the appreciable amount of venereal disease now treated by general practitioners, the actual incidence of the disease must be considerably higher than the clinic figures suggest. According to the chief medical officer's report, this rise is 'undoubtedly connected with a widespread misplaced faith in a "one shot" treatment and a consequent reluctance to attend for post-treatment observation and tests of cure'. Penicillin-resistant strains of gonococci are now being encountered, and it is clear that penicillin 'cannot by itself make a lasting impression on the incidence' of the disease. One of the results is that asymptomatic chronic gonorrhœa, once almost the prerogative of the female of the species, is now becoming more common in the male.

Two other points in the chief medical officer's report are worthy of comment. One is that over 50 per cent. of the teen-age prostitutes remanded in custody to Holloway women's prison for a medical report were found to have gonorrhœa. Most of them were not only unaware of their condition but were also quite ignorant of the dangers of venereal disease. The other, to quote the report again, is that 'out of the small number of male cases of early syphilis diagnosed in 1957 at a large clinic in London, no less than 60 per cent. of the total occurred among male homosexual patients'. These two points raise moral as well as medical issues, but as citizens, practitioners cannot but be worried by the increase in juvenile patients, which is not confined to Holloway, but is being reported from clinics in London and the provinces. As doctors they can help by ensuring that every case of suspected gonorrhœa is referred to the nearest venereal clinic, or alternatively ensuring that, if they undertake treatment themselves, this will be adequate and complete—and not merely a perfunctory injection of penicillin.

Cycling to Health

BICYCLING is Dr. Paul D. White's recipe for health. It suffers from the fundamental drawback in his own country that anyone who is unwise enough to venture on a bicycle on an American highway is unlikely to survive very long to enjoy health of any description. To remedy this state of affairs a committee for safe bicycling was set up in Massachusetts in 1957 and worked to such good purpose that, according to Dr. White (*New Engl. J. Med.*, 1958, **259**, 499), by the end of the year the State Legislature had passed a bill allocating funds to build a 'safe bicycle path' on the Island of Nantucket. This path was duly opened last August and Dr. White expresses the hope that this will inspire a nation-wide campaign for the building of such paths 'to schools, to railroad or bus stations and to shopping areas, and then to link them up by the establishment of safe paths alongside secondary roads' from one community to another.

It is only right that, as the pioneer of the automobile, the United States should now come to the fore as the advocate of the bicycle, and the campaign will be watched with more than passing interest by the inhabitants of these old-fashioned Islands. It may well be that we ourselves may become the next target in this 'cycling to health' campaign, as Dr. White reports that a Society for Medical Studies of Bicycling has recently been founded in France. One intriguing possibility of this new Transatlantic development is that it may yet allow us to enjoy a trip to the United States on the miserable allowance allotted by the Treasury. Some enterprising travel agency may one day be able to advertise cycling tours of the States, its motto being not 'See Naples and die' but 'See America and live'!

Practical Dietetics

IF, as we believe to be the case, the future of good general practice is largely dependent upon the general practitioner undertaking an increasing amount of the care of his patients, it is essential that he should be given every possible facility to allow him to do this. It is with a view to helping him in this task that during the last few years we have published several series of articles dealing with the practical side of general practice. These have included 'The Doctor's Surgery', 'Equipping the Surgery', and 'Minor Surgery'. Throughout 1959 we propose to publish another series which we hope will be of equal value—on 'Practical Dietetics'. The aim of this series, the first of which is published on p. 115, is to provide authoritative, yet practical, guides to the planning and supervision of those diets which may be necessary for his patients. There is a tendency for both patients and practitioners to make rather heavy weather of 'diets'. Often, hospitals and consultants are responsible for this attitude by not issuing clear enough instructions or, alternatively, not realizing that what is possible dietetically in hospital is wellnigh impossible in the home. Our new series, we hope, will overcome this difficulty and show practitioners and, through them, housewives how a patient's dietetic requirements can be met within the means and facilities available in every normal home.

VITAMIN A

By THOMAS MOORE, Sc.D.

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VITAMIN A, $C_{20}H_{30}O$, is a colourless, fat-soluble alcohol which is produced by animals from the yellow plant pigment carotene, $C_{40}H_{56}$, by processes which amount to the addition of water. Carotene, as its name implies, gives colour to the common carrot, but the provitamin is widely distributed in all green, and in most yellow, vegetable tissues. It is never produced by animals, but a proportion of the ingested pigment may escape conversion to vitamin A and pass unchanged into animal tissues. Several isomeric forms of carotene are known, but of these the β-form is both most efficient in serving as a provitamin, and most widely distributed. In many animal and vegetable materials, however, the pigment, xanthophyll, $C_{40}H_{56}O_2$, which is inactive as a provitamin, preponderates over carotene. Thus the familiar pigments of egg yolks and marigold blossoms are mainly xanthophylls. A second form of vitamin A, not an isomer but formed by the loss of two hydrogen atoms, is found in fresh-water fish. There is no evidence, as yet, that this vitamin A_2 is of any importance to the clinician.

CHEMISTRY

The absorption spectrum of vitamin A has an intense band in the ultra-violet region at 328 mμ. Solutions of the vitamin in chloroform produce an intense blue colour with antimony trichloride. Accurate methods for the estimation of the vitamin are based on these two properties. In histological preparations the presence of vitamin A may be revealed by its yellow-green, transient fluorescence under ultra-violet irradiation.

In the body vitamin A may be present as the free alcohol, which predominates in the blood plasma, or as vitamin A esters, which predominate in the liver. Both the 'free' alcohol and the esters, however, can form lipoprotein complexes. On a quantitative basis the liver is the body's main storage site for vitamin A. Massive reserves, sufficient to last for years, can be accumulated in this organ. Smaller amounts are found in the blood, kidneys, adrenals, lungs, eyes and body fat, but in most other tissues only traces can be detected. It is important to realize that the distribution of vitamin A in the body is peculiar to itself, and that it by no means runs parallel to the distribution of fat, or even of other fat-soluble vitamins. Certain curiosities in vitamin A distribution, such as its high concentrations in the kidneys of cats (Lowe, Morton and Vernon, 1957), eyes of shrimps (Fisher, Kon and Thompson, 1951) and body fat of eels (Edisbury, Lovern and Morton, 1937) present interesting problems to specialists in comparative biochemistry.

Chemical oxidation of vitamin A produces an aldehyde, known as retinene or retinaldehyde, which can be readily reduced back to vitamin A in the animal body. By synthetic methods another oxidation product, vitamin A acid, may be obtained. In experimental animals this acid has been found to possess some of the biological properties of vitamin A. Unlike retinaldehyde, however, it does not undergo reduction in the tissues to vitamin A alcohol. Both vitamin A alcohol and vitamin A aldehyde, and presumably vitamin A acid as well, are susceptible to *cis-trans* isomerism. Thus the chemical, physical and biological properties of the vitamin depend upon whether the side-chain of the molecule is extended straight, in the *all trans* position, or is bent at various unsaturated linkages to form *cis* isomers (fig 1). Conversion between the various isomers can take place in the body, at least to a limited extent.

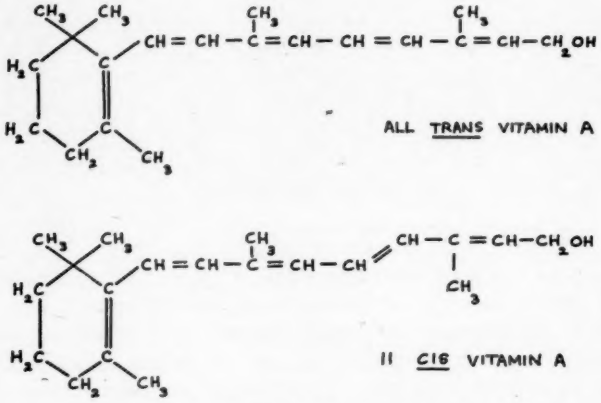

FIG. 1.—Structural formulæ of all *trans* and 11-*cis* vitamins A.

MODE OF ACTION

Vitamin A appears to act in at least two distinctly different ways, according to whether it is present in the retina, or in the rest of the body. It is ironical that we know much more about the action of the 0.1 per cent., or less, of vitamin that is present in the retina than of the 99.9 per cent. that is present elsewhere.

In the retinal rods vitamin A is converted by enzymes to retinaldehyde which then combines with the protein opsin to form rhodopsin, long known as visual purple. The key position of this pigment in vision presumably depends upon its instability to light, which severs the link between the retinaldehyde and protein. A simple form of the rhodopsin system of Wald (1935, 1951), to which Morton (1944) made a vital contribution in identifying retinene with vitamin A aldehyde, is shown in figure 2. The system was later complicated by the discovery by Hubbard and Wald (1952) that the vitamin not only undergoes oxidation and reduction, but also *cis-trans* isomerism.

Thus, to combine efficiently with opsin retinaldehyde must assume its 11-*cis* form, whereas retinaldehyde freshly liberated from rhodopsin appears to be in the *all trans* form. An interesting point is that neither rhodopsin nor retinaldehyde has been found in any other part of the mammalian body.

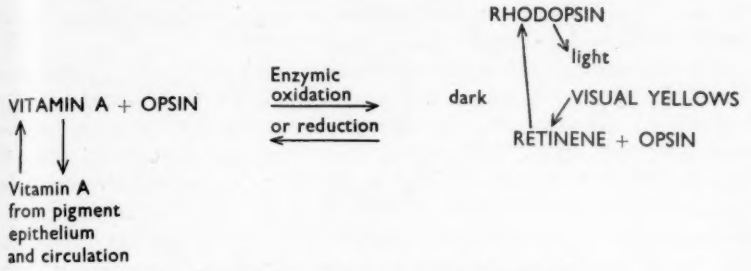

FIG. 2.—Wald's rhodopsin system in simplified form.

This would suggest that opsin is unique in its ability to combine with, and so temporarily stabilize, retinaldehyde. Plack, Thompson and Kon (1958), however, have made the disconcerting discovery that the aldehyde is sometimes present in fish eggs.

In the general system the biochemistry of vitamin A remains obscure, although we have some knowledge of the biochemical effects caused by deficiency of the vitamin. Thus, xerophthalmia, the classical sign of vitamin A deficiency, is caused by a drying up of the membranes of the eye, which in turn can be traced to failure in the activity of mucus-secreting cells and their replacement by scales of keratin. A fault in the formation of muco-polysaccharides must be implicated, either closely or distantly related to the biochemical point of action of the vitamin. These changes can affect membranes throughout the body. Abnormalities in bone formation, studied by the late Sir Edward Mellanby (1944) are probably traceable to the same biochemical lesion.

A clue to the problem of the different roles of vitamin A in the retina and in the general system may be provided by vitamin A acid. This substance can promote growth in rats deficient in vitamin A, but according to Wald (1958) it cannot cure their defective dark adaptation.

SYMPTOMS AND SIGNS OF DEFICIENCY

The two classical lesions caused in man by lack of vitamin A are night blindness and xerophthalmia. Although these abnormalities often occur together they must be regarded as separate, one affecting the specialized retinal system and the other the general system. A lesion less severe than xerophthalmia takes the form of Bitot's spots, seen as chalky or foamy triangular specks under the conjunctiva at the corners of the eyes. More severe lesions take the form of keratomalacia, invasion of the eyeball by pus,

and the loss of sight by perforation. Besides affecting the eyes lack of vitamin A can also cause skin lesions characterized by hyperkeratosis, such as 'phrynoderma' or 'toad skin'. Frank cases of xerophthalmia are seldom seen in Great Britain. Defective dark adaptation is less rare, but even when it is detected there is always a possibility of some cause other than lack of vitamin A. Similarly, skin abnormalities involving hyperkeratosis can result from nutritional deficiencies other than of vitamin A.

In experimental and farm animals the range of lesions is wider. Keratinization of membranes is widespread, and often followed by secondary infections. In deficient rats, for example, infections are common in the respiratory and urinary tracts, and in the salivary glands. Abnormalities in bone growth, with defective modelling, can be produced experimentally in dogs or rabbits, and also occur occasionally under practical farming conditions in cattle which are fed upon sugar beet pulp. In the skull the malformed bones allow insufficient space for the brain and nerves. There is also a rise in the cerebrospinal fluid pressure, but this appears to be due to an increased secretion of fluid rather than secondary to the bony changes (Woollam and Millen, 1956). In pregnant pigs, rats and rabbits deficiency of vitamin A can cause a variety of congenital defects in the fœtuses, including absence of the eyes, cleft palate, malformations in the heart and urinary system, and hydrocephalus.

In a short article it is impossible to describe adequately all the known lesions in avitaminosis A in different species. A warning may be given, however, against undue confidence in assuming that vitamin A deficiency in the human subject must always reveal its presence by the development of xerophthalmia or Bitot's spots. Experimental rats may succumb to the effects of deficiency either with or without developing xerophthalmia. An equally irregular incidence of xerophthalmia in human avitaminosis A would not be surprising. Moreover, although bone lesions have not been reported in deficient human subjects, in contrast to findings in experimental animals, we shall see later that human bones are affected by toxic excess of vitamin A no less than those of experimental animals.

DAILY REQUIREMENTS

Assessment of human requirements for vitamin A is complicated by the fact that most diets will contain both the preformed vitamin and also carotenes. The provitamins are absorbed less efficiently than the preformed vitamin, and some allowance for this inefficiency must be made. Absorption will be better from some sources than others, but as a rough rule carotene units are usually divided by a factor of three to convert them to vitamin A units. Both the vitamin A and carotene units were originally based on the requirement of rats, and human requirements are therefore reckoned in thousands of these small units.

Evidence on daily requirements has been derived from two main sources. First, estimations have been made of the vitamin A values of diets eaten in

countries, such as India, where frank signs of vitamin A deficiency are less rare than in Britain. From comparisons of the incidence of lesions in populations receiving the different diets conclusions can be drawn as to the intake of vitamin necessary to prevent the lesions. Secondly, there has been a

Children (15 years and under)		Vitamin A	1,500 i.u. or
		Carotene	4,500 i.u. or
	'mixed diet'	⅓ vitamin A	
		⅔ carotene	3,000 i.u.
Adolescents and adults		Vitamin A	2,500 i.u. or
		Carotene	7,500 i.u. or
	'mixed diet'	⅓ Vitamin A	
		⅔ Carotene	5,000 i.u.
Pregnancy		Vitamin A	3,000 i.u. or
		Carotene	9,000 i.u. or
	'mixed diet'	⅓ Vitamin A	
		⅔ Carotene	6,000 i.u.
Lactation		Vitamin A	4,000 i.u. or
		Carotene	12,000 i.u. or
	'mixed diet'	⅓ Vitamin A	
		⅔ Carotene	8,000 i.u.

TABLE I.—Daily requirements of vitamin A for humans, as assessed by the British Medical Association (1949-50).

number of experiments in which volunteers have been restricted to diets deficient in vitamin A until defects in dark adaptation have developed, and have then been cured by graded doses of vitamin A or carotene. An experiment on conscientious objectors, carried out at Sheffield during the 1939-45 War, was probably the most ambitious venture of this kind, but was less successful than was hoped because of the very long periods, up to two years, found necessary to deplete the original liver reserves (Hume and Krebs, 1949).

About 1,250 i.u. of vitamin A will correct defective dark adaptation in a depleted, but otherwise healthy, man. In assessing the daily requirement a safety margin 'of 100 per cent.' is allowed, making 2,500 i.u. For carotene the requirement, three times greater, is assessed as 7,500 i.u. These requirements must obviously be modified for children, and for pregnant and lactating women. Moreover, human diets will seldom contain only vitamin A or carotene, but usually a mixture. The best attempt to allow for all these factors has been made by the nutrition committee of the British Medical Association (table I).

Higher doses may sometimes be advisable in illness. In subjects acutely deficient in vitamin A, from dietary causes, doses of up to 2000 i.u. of vitamin A per kg. of body weight daily may be administered with the aim of promoting a rapid cure. In this country, however, low liver reserves of vitamin A are probably due much more often to various diseases than to a defective diet. Estimations of liver reserves at necropsy have indicated, for example, that in appendicitis and cancer the average loss of vitamin A may amount to about 50 per cent. of the original reserve, in pneumonia 70 per cent. and in chronic nephritis 90 per cent. Even if vitamin A therapy cannot be expected to alter the course of the disease it may seem advisable to make

good the losses of vitamin that are being incurred, or failing that to build up the reserves during convalescence. Total doses of about 500,000 i.u., given at the rate of about 20,000 i.u. daily, should provide adequate replenishment, provided that the absorption of the vitamin is not defective.

In passing, reference may be made to the well-established influence of sex on the vitamin A status. Observations by many workers, reviewed elsewhere (Moore, 1957), have indicated, for example, that xerophthalmia is much more common in boys and men than in girls and women, that blood levels of vitamin A tend nevertheless to be higher in men than in women, and that vitamin A appears to be absorbed from the intestines more rapidly by men then by women. A suspicion must arise that the vitamin A requirements of men are somewhat greater than those of women. A direct experimental comparison of the requirements of the two sexes, however, would be so laborious and so inaccurate that the possibility of this point ever being successfully investigated seems unlikely.

FOODS CONTAINING VITAMIN A AND CAROTENE

In the compilation of tables of vitamin A values the same complication holds as in assessing requirements, with the necessity of dividing sources of the vitamin and its provitamins into separate lists. Usually this can easily

Food	Vitamin A i.u./100 g.	Food	Carotene i.u./100 g.
Halibut-liver oil	4,000,000	Carrots, mature	20,000
Cod-liver oil	200,000	Spinach	13,000
Liver, sheep	45,000	Spinach beet leaves	11,000
Liver, ox	15,000	Carrots, young	10,000
Liver, pig	5,000	Cress	8,000
Liver, calf	4,000	Kale	8,000
Butter	3,500	Sweet potato	6,000
Cheese (whole fat)	1,500	Watercress	5,000
Eggs, hen	1,100	Apricot	2,000
Kidney, ox	1,000	Lettuce	2,000
Salmon, canned	250	Tomato	1,200
Milk, summer	150	Peach	800
Herrings, fresh	100	Brussels sprouts	700
Milk, winter	75	Cabbage	500
Beef or mutton	20	Maize, yellow	350

TABLE II.—Vitamin A or carotene contents of various foods. Carotene values must be divided by 3 to convert to vitamin A values.

be done, because either vitamin A or carotene clearly predominates. Thus, all vegetables are quite free from preformed vitamin A, whilst butter is perhaps the only important animal food in which the contribution by provitamins cannot be neglected. Liver, and oils derived from it, are pre-eminent as sources of preformed vitamin A. Milk, butter, cheese, eggs and fat fish, however, can provide adequate supplies of vitamin when freely consumed. Carrots and dark green vegetables, such as spinach and watercress, are the foods richest in provitamins. Among animal foods, pork, bacon and lard are defective in vitamin A. Among vegetable foods all cereals, with the exception of yellow maize, and all oils, excepting red-palm oil, contain

no more than traces of provitamins. Margarine is fortified with vitamin A to be equivalent to butter. Ordinary potatoes are also negligible as sources of carotene, although yellow sweet potatoes, a different plant, are quite rich. The very wide ranges of potency found in both animal and vegetable foods may be seen from the brief lists of typical values given in table II. It must be realized, of course, that the importance of foods as sources of vitamin A, as for other nutrients, will depend not only upon the concentration of vitamin, but also on the amount of the food which can be conveniently eaten. Milk, for example, is not a rich source of vitamin A, but no anxiety need be felt about the vitamin A intake of a child, or patient, subsisting mainly on this food.

THERAPEUTIC USES

Mode of administration.—Preformed vitamin A is miscible with all fatty media, whereas carotene is only sparingly soluble in oils and fats. As already stated, vitamin A is absorbed more efficiently than carotene from the intestines, and it is therefore preferable to the provitamin for therapeutic use. In the absence of severe intestinal disorders there is no need to give vitamin A by injections, since it is absorbed much more efficiently by the oral route. Absorption from aqueous emulsions is slightly better than from oily solutions after oral administration and decidedly more efficient after administration by injection. Medicinal paraffin has been shown to depress the absorption of carotene, but paraffin has little effect on the absorption of preformed vitamin A.

The occurrence of *skin lesions* in subjects deficient in vitamin A has already been mentioned. Presumably on the basis of this observation massive dosing with vitamin A has been applied by many dermatologists to the treatment of certain skin diseases, and particularly those conditions involving hyperkeratosis. There seems little evidence that the diets of patients with these diseases are deficient in vitamin A, and some fault in the absorption of the vitamin, or more probably in its distribution and efficiency of action in the body, is therefore suspected. The diseases treated have included such rarities as Darier's disease, ichthyosis and pityriasis rubra pilaris (Leitner and Moore, 1946), but Maynard (1941) and others have claimed success in the treatment of common acne. The doses recommended are high, up to 200,000 i.u. daily, and a warning must be given at once against the expectation of dependable results. A typical finding is that some patients are improved, or in some diseases completely cured by vitamin A, but that others fail to respond. Often the benefit to the skin only persists for as long as administration is continued.

A recent report by Fisher (1955) on the treatment of ichthyosis vulgaris with vitamin A may be mentioned both because it provides a good example of the degree of success to be expected, and also because it illustrates the significance of 'group differences' in vitamin A metabolism.

In children or adults, who were treated with 50,000 to 400,000 i.u. of vitamin A daily, the scales usually disappeared from the skin within periods of three to forty

weeks. Some cases, however, were described as 'improved', presumably with persistence of scaling. Estimations of vitamin A in the blood plasma, before dosing started, gave a lower average for the ichthyotic patients than for a group of patients with sound skins. A considerable overlap was found, however, between individual values in the two groups. Thus the higher values in the ichthyotic group, in spite of the lower average, substantially exceeded the lower values in the control group. Estimations made after treatment showed the same relationship between the groups, but with all individual readings at much higher levels. Improvement, it is important to note, occurred irrespective of whether the original blood level of vitamin A had been low, or had been well within the control range. Moreover, in order to effect improvement it was necessary to raise the plasma level beyond the range normally found in untreated subjects. When administration was stopped scaling generally reappeared as soon as the blood level of vitamin A had returned to within the normal range.

These findings seem important in raising doubts as to how far the individual vitamin A status, at least as indicated by the blood level of vitamin, can be relied upon as a guide to whether treatment with the vitamin will be beneficial. The problem, moreover, does not seem to be limited to skin diseases. Thus Roels, Debeir and Trout (1957) have found a low average, but again with individual values overlapping into the control group, in African natives showing Bitot's spots, an accepted sign of vitamin A deficiency. On the evidence so far available therefore, we must conclude that complete exhaustion of the body's reserves of vitamin A is not an essential condition before vitamin A therapy can be beneficial. It seems possible that many new fields for the application of vitamin A therapy may eventually be opened up. For the present, however, both the recognition of cases likely to benefit, and the realistic assessment of any improvement as the result of therapy, present formidable problems.

During the 1939-45 War the role of vitamin A in dark adaptation inevitably attracted attention. Heavy dosing with vitamin A was obviously worth a trial for improving the night vision of sailors and airmen, but it is doubtful whether any improvement beyond the normal range of sensitivity was achieved.

TOXIC EFFECTS

Vitamin A resembles vitamin D in being toxic when given in great excess. Moreover, as with the antirachitic vitamin, the lesions produced are clearly related to those observed in deficiency. Thus the state of hypervitaminosis appears to be caused by the vitamin acting in its normal manner, but without being subject to the influences which must normally control its action. Skeletal fractures in rats given excessive doses of vitamin A have been known for over thirty years. The clinical effects of hypervitaminosis A, however, have been known even longer, since Arctic explorers, even in Elizabethan times, were aware of the dire effects of eating the liver of polar bears. Rodahl and Moore (1943) found that the liver of this animal was so rich in vitamin A as to make hypervitaminosis seem an inevitable consequence of its consumption.

Reports of hypervitaminosis A under ordinary domestic conditions have come mainly from America and from France. All the incidents have been

due to greatly excessive intakes of therapeutic preparations of the vitamin. In some cases infants and children have been overdosed for no purpose at all, except for the fallacy that 'one can never have too much of a good thing'. Two types of lesions have been observed. Marie and See (1951) noticed that when young infants were given single doses of about 300,000 i.u. of vitamin A, twelve hours later they developed a mushroom-like protuberance of the fontanelle, accompanied by vomiting. The disturbance was only temporary, and was presumably due to an increased secretion of cerebrospinal fluid. We have already seen that the same increase in pressure can result from avitaminosis A, which suggests that either the absence or excess of vitamin can disturb the delicate balance of the chorionic cells in excreting the correct amount of fluid. The second type of injury to result from 'aimless' dosing is caused by chronic excess. An early case was described by Josephs (1944). A three-year-old boy, who had received halibut-liver oil equivalent to 240,000 i.u. of vitamin A daily from the age of three months, became seriously ill. The syndrome included precocious skeletal development, enlargement of the liver and spleen, hypoplastic anæmia, clubbing of the fingers and coarse sparse hair. The blood level of vitamin A was many times higher than the normal average. Discontinuation of dosing soon corrected most of the abnormalities, and allowed the blood vitamin A to return within the normal range.

Cases in which the administration has not been aimless have all arisen from the treatment of skin diseases. Gerber, Raab and Sobel (1954), for example, eventually arrived at a diagnosis of hypervitaminosis A in a 28-year-old woman, who had a history of eight years of persistent illness, for which she had been treated on ten occasions in different hospitals. She suffered from headaches, a coarse and itching skin, blurring of vision and diplopia, and stiffness and pain in the spine and limbs. The liver was somewhat enlarged. The skull was bulged in the right temporal area, and a tantalum plate had been fitted after an operation for sub-temporal decompression. The patient was well nourished, but walked with a stoop and had pain and difficulty in moving. X-ray studies indicated extensive skeletal abnormalities, including calcification of the ligamenta flava and of the infrapatellar ligaments. Previous diagnoses had included brain tumour, viral radiculo-encephalitis, psychoneurosis and infective arthritis, whilst investigations had been made to exclude Addison's disease, dermatomyositis and hepatitis. Sobel and his colleagues, however, elicited the vital information that the patient, for the whole duration of her illness, had been taking no less than 500,000 i.u. of vitamin A daily for the control of ichthyosis. On discontinuing the excessive dosage the condition of the patient rapidly improved. Pruritus ceased after seventeen days, improvement in the skin was noticed after one month, and after two months there was no more spontaneous pain in the bone and spine. It took several months, however, for the level of vitamin A in the blood to fall within the normal range.

Fortunately, cases of hypervitaminosis A have been comparatively rare.

It is perhaps a reflection on the lavish nutritional standards in America, however, that in recent years reports of cases of hypervitaminosis A have outnumbered those of frank avitaminosis A, as characterized by the classical xerophthalmia.

Hypercarotenosis.—Disconcerting symptoms, but with less effect on the general health, have also been reported in subjects who have ingested excess of carotene, particularly in the form of carrots. The skin becomes decidedly yellow, but jaundice is ruled out by the absence of colour in the sclerotics. It seems probable that abnormal yellowness will appear in any subject if a sufficient excess of carotene is taken, but Cohen (1952) and others have found that hypothyroidism increases the liability to pigmentation. Almond and Logan (1942) gave an interesting account of cases of hypercarotenosis caused during the 1939-45 War by the intensive propaganda for an increased consumption of carrots. Some women developed a liking for the vegetable which amounted to a craving, and consumed 2 to 3 kg. weekly. Unsuspecting practitioners diagnosed jaundice, pernicious anæmia or cholelithiasis before the true cause of their yellowness was recognized. The yellowness generally disappeared rapidly after the excessive consumption of carrots had been stopped. McGonaghey (1952), however, reported the case of a woman who preferred, after assurance that her condition was not serious, to remain permanently yellow rather than to deny her craving for carrots.

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VITAMIN D

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VITAMIN D is unique among the vitamins in that, in Nature, the greater part of it is not taken by mouth but through the skin. As long ago as 1890, in *The Practitioner*, Palm reported on the distribution of rickets throughout the world and stated: 'The reader is asked to review the facts as to the distribution of the disease in the light of the theory that *sunlight* is essential to the healthy nutrition of growing animals and that a deficiency of it characterizes the localities or conditions of those who suffer from rickets, and is the most important element in the etiology of the disease'. Palm's work is probably the earliest example of the use of epidemiology to pinpoint correctly the cause of a deficiency disease. A brilliant train of research on the aspects of vitamin D was initiated towards the end of the 1914-18 War, with which the names of McCollum, Mellanby, Hess and Unger, Chick and Hume, and finally Bourdillon, will always be associated; but the triumph of these investigators should never blind us to the significance of Palm's work. The present need to take vitamin D by mouth is determined not so much by a shortage of the livers of cods and similar foods upon our table, as by smoke, and the shadows cast by cities upon their streets, and by the short periods spent by some children and by many women, before and during pregnancy, in the open air. True, we do not know how much, or rather how little, skin we need to expose in our inclement clime, but even in Palm's time rickets was not common in rural areas, and babies wear fewer clothes and are in the open more now than they were then. Future generations may well regard our present preoccupation with oral vitamin D as symptomatic of a sickness of civilization, rather than of a dietary deficit.

THE ROLE OF VITAMIN D

The functions of vitamin D in the body are far from clear. The bony changes of rickets are dependent upon a decrease in the amount of calcium and phosphorus available for calcification, and vitamin D is apparently involved both in the absorption of calcium from the gut and in the tubular reabsorption of phosphate from the kidney, and in the actual deposition of both of these in bone. Nor may these be its only functions. Wilhelm (1958) has reported that vitamin-D-deficient rats show less adenosine triphosphoric acid in their muscles than do controls, whereas rats intoxicated by vitamin D show an excess; and Jonxis *et al.* (1952) observed that children with rickets excreted more amino-acids in their urine than did normal children, and that this could be corrected by administering calciferol. Even the role, or roles, of vitamin D in bone formation still awaits clarification. It has been shown that phosphorylated vitamin D enhances the action of alkaline kidney

phosphatase (Zetterstrom, 1951) and it has been suggested that in growing bone phosphatase hydrolyses esters of phosphoric acid, to release phosphate which reacts with calcium in the growing bone to form tricalcium phosphate. But phosphatase is not present at the actual site of deposition of bone (Wilhelm, 1958) and it becomes increasingly likely that its main role is in the development of the organic matrix which is to be ossified. An analogous situation probably prevails also in calcifying teeth (Ten Cate, 1958). Wilhelm, using labelled sulphur in autoradiographic studies of the bones of growing rats, reports that there is normally at the site of deposition of bone salt some unidentified substance, which is absent in rachitic rats but reappears within two hours of the administration of vitamin D. Possibly the increase in alkaline phosphatase that occurs in rickets is a sign of a compensatory overproduction of organic matrix.

THE REQUIREMENT OF VITAMIN D

An aphorism fashionable among nutritionists is: 'Enough is better than a feast'. This applies particularly to vitamin D. Four hundred international units of vitamin D daily is a satisfactory intake for any normal child. It is also enough for a premature infant, in whom an intake above 250 international units (i.u.) does not lead to any increase in serum calcium or reduction in phosphatase levels (Harrison, 1953). Probably 100 i.u. daily is enough to protect from rickets, but 400 i.u. daily ensures optimal nutrition in normal children, and this is in fact the amount recommended for most children by the British Medical Association's committee on nutrition and other authoritative bodies,

Many pre-school and most school-children consume much less than 400 i.u. and they suffer no observable ill-effects, but it should be remembered that they are often in the open air and that their intakes of calcium and phosphorus, which are obviously relevant to the issue, are as satisfactory as those of children in any country in the world and better than most. Finally, hitherto the vitamin D intake of many babies has been very high and they have presumably therefore accumulated a considerable reserve by the end of the first year of life; that vitamin D can be stored efficiently is clear from the success that has followed the practice of 'Stosstherapie' in which one or two massive parenteral doses of the vitamin, given early in life, effectively protect from rickets.

Adults normally need some vitamin D. It would seem that they get enough from the sun and from their daily diet but the requirement rises markedly during pregnancy and lactation, because calcium and phosphorus are needed for fœtal growth and lactation. In this country, however, many women take no special source of vitamin D at such times yet osteomalacia does not result. But this does not preclude the possibility either that the mother's bones may have been drawn upon for minerals, or that the child may be born with a suboptimal reserve of vitamin D. During pregnancy and lactation 400 units daily are probably adequate, although 800 i.u. were

advised during lactation by the British Medical Association committee in 1950.

THE STORY OF THE PREVENTION OF RICKETS IN BRITAIN

If Palm's work is construed to mean that the rickets which he observed arose out of a sickness of our civilization, then we have been remarkably efficient in reducing, indeed almost eliminating, this manifestation of its sickness. The manner of this reduction can be conveniently set out in three parts. During the first stage, in 1868, Gee estimated that at least one-third of London children suffered from severe rickets (Harris, 1955); this stage had ended by 1933 when Chisholm (1933), in Manchester, and Spence (1934), in Newcastle, x-rayed reasonably representative samples of children and reported an incidence which, for comparative purposes, may be put at rather more than five per cent. During those sixty-five years there had obviously been a reduction in rickets but it is difficult to assess just when it took place because such representative surveys as were made (as opposed to reports on the incidence of rickets in hospital patients) were on children of varying ages and environments; moreover, they were based on clinical criteria which must have varied from examiner to examiner.

The second part of the reduction extends from 1933 to 1942 when the British Pædiatric Association carried out a survey of over five thousand children in Britain and Ireland. The incidence of active rickets diagnosed radiologically was then found to be 0.5 per cent. or less. The final stage extends to the present day. On behalf of the Joint Advisory Committee on Welfare Foods an inquiry was made in 1956 of a number of pædiatricians and medical officers of health throughout England, Scotland, and Wales as to what cases of rickets, radiologically or biochemically confirmed, they had encountered in the previous two years. In all, 24 cases were reported and, although it is impossible to calculate the incidence because the magnitude of the related child population is unknown, it was probably considerably less than 0.05 per cent.

These three periods are also characterized by certain differences in methods of preventing rickets. In the first such measures as were taken involved deliberate action by the parent: for example in the administration of cod-liver oil. In the second what the Germans call 'silent prophylaxis' was initiated on a large scale by the vitaminization of all the dried milk made by one commercial firm; hitherto it had merely made limited supplies available to public health departments. In the third, 'silent prophylaxis' became nation wide, in that all dried milk destined for consumption by babies was vitaminized, as were also most infant cereals; in addition, National Cod-Liver Oil as well as vitaminized National Dried Milk became available free or at specially cheap rates for small children, under the Welfare Foods Scheme.

The improvements that occurred in these three periods cannot be

ascribed solely to increased consumption of vitamin D. Dietary improvements, including an increased intake of calcium, played some part, as did also the healthier and more open-air life lived by children. But undoubtedly it was the most important factor.

VITAMIN D INTAKES BY INFANTS

In 1951, and again in 1955, large-scale surveys were carried out for the Ministry of Health of the uptake (*inter alia*) of National Cod-Liver Oil compound. It was reported that during the week of survey 36 per cent. of children under one year took the product daily, but by the age of five only 21 per cent. did so; 54 per cent. of children born in 1955 took no cod-liver oil compound during the week of survey, and by the fifth year this proportion had risen to 68 per cent. Even when allowance was made for the part played by proprietary preparations it was clear that there must be many children in whom deliberate prophylaxis was non-existent or at best intermittent. Berry *et al.* (1955) inquired into the feeding of 37 children under two years in Salford who took no cod-liver oil or other vitamin D preparation, and found that 27 of them had had a greater or lesser consumption of one or other brand of fortified milk. These workers described dried milk as the second string to the bow of prevention of rickets, and evidence advanced by Dykes in Luton and by the Public Health Department of Bristol (Appendices 3 and 4, Report of the Joint Sub-committee on Welfare Foods, 1957) clearly confirms this. Fortified infant cereals, as these same reports show, also played a part in protecting about 12 to 14 per cent. of babies who were consuming neither fortified milk nor cod-liver oil.

Indeed, the steps taken to prevent rickets led to a situation in which children taking a vitamin preparation, fortified milk, and a fortified infant cereal, might easily take too much vitamin D. This point was made by Creery and Neill (1955) and by Berry *et al.* and was endorsed by a Conference on Hypercalcæmia of the British Pædiatric Association (1956); and one of the main tasks of a subcommittee subsequently called to advise on welfare foods was to rectify this situation. Lightwood (1952) had reported cases of a disease, infantile hypercalcæmia, hitherto not observed in Britain and, although the Advisory Subcommittee on Welfare Foods clearly appreciated that excess of vitamin D might not be the sole or even the prime cause of this, it nevertheless advised major reductions in the vitamin D content of the main supplies of vitamin D to small children. This advice was accepted, not merely by the Government in respect of the products for which it is responsible, but also by the manufacturers of proprietary dried milks and cereals.

Infantile hypercalcæmia is characterized by vomiting, anorexia, constipation, growth failure, and raised levels of calcium and cholesterol in the serum (Stapleton, MacDonald, and Lightwood, 1957); it may present other much more serious manifestations, related largely to metastatic calcification,

and may end in death. Although much of the syndrome is suggestive of vitamin D intoxication, some features are inconsistent with this hypothesis. For example, Forfar *et al.* (1956) administered large doses of vitamin D to hypercalcæmic infants without evidence of ill-effects. In addition, such inquiries as have been made into the sources of supply of vitamin D of these infants have not revealed a pattern notably different from that of bottle-fed infants in general, but practically all of them are bottle fed, and it is significant that cow's milk contains about four times as much calcium as human milk. Finally, the high level of serum cholesterol has not been satisfactorily explained. Sinclair (1956) has advanced the tentative hypothesis that it is due to the fact that cow's milk contains more saturated and less polyunsaturated fat than does human milk but, although preliminary tests of this hypothesis are encouraging, proof has not been advanced. In the meantime the reductions in vitamin D advised by the Subcommittee on Welfare Foods have been implemented so that we have, in effect, embarked on a major nutritional experiment on a country-wide scale. It is too early yet to form an opinion, but already one pædiatrician has reported his impression of a marked reduction in the incidence of hypercalcæmia (Graham, 1958). Let it be said, however, that even if the disease were eliminated, this does not necessarily dispose of the hypothesis advanced by Sinclair.

As already noted, reductions have been made in the vitamin D content of the three main sources available to infants. On average, cod-liver oil now contains about 100 i.u. per g.; fortified dried milk about 100 i.u. per ounce of dried powder (350 i.u. per 100 g.), and infant cereals about 300 i.u. per ounce (1,070 i.u. per 100 g.). In assessing how much a child is receiving, it may be taken that the optimal intake of 400 i.u. is present in one teaspoonful of cod-liver oil, in one and a half pints (850 ml.) of milk mixture made from dried milk in accordance with directions, and in about 17 teaspoonfuls of infant cereal. It is also present in some infants' rusks (but the container should be examined to make sure that the particular product consumed is in fact fortified). In practice few infants will be on one source only, and the sum total of vitamin D may be more than 400 i.u. It is probable that up to 1000 i.u. daily is harmless (although our ignorance of the role of vitamin D in infantile hypercalcæmia makes a dogmatic statement impossible); on the other hand intakes below 200 i.u. are too low, although here again, infants vary enormously in their need for vitamin D. From evidence supplied to the Advisory Committee on Welfare Foods it seems that the vast majority of babies' intakes will lie well within these limits.

VITAMIN D INTAKES BY OLDER CHILDREN

The Ministry of Health inquiries of 1951 and 1955 indicated that many children above the age of one year received no special vitamin D preparation. As infant cereals and fortified milks are rarely consumed after the age of 18 months, there is a marked fall after that in the dietary content of vitamin D. It was recognition of this fall that led to the compulsory fortification of

margarine with 80 to 100 i.u. of vitamin D per ounce (280 to 350 i.u. per 100 g.). When margarine rather than butter is consumed, intakes by pre-school children average about 70 i.u. daily, but when butter is consumed, the average is only 35 to 40 i.u. Older children eat more food (a boy aged 16 eats about twice as much food as a pre-school child) and their intake of vitamin D is therefore greater. If the amount of vitamin D consumed by these children were not sufficient to protect from rickets, the disease would be common among those who take no vitamin preparation. Whether sufficient vitamin D is taken for optimal growth is less certain. There are, for example, differences in the growth rates of children of different socio-economic environments, which could be ascribed to differences in the amount of vitamin D which children receive; but on the whole, children of the higher income groups, in whom growth is most rapid, consume butter rather than margarine.

VITAMIN D INTAKE BY ADULTS

Comparatively few foods are rich sources of vitamin D and of these the most important one, margarine, with about 300 i.u. per 100 g., owes its content of the vitamin to the fact that it is there by law. Of other foods, the humble sardine, with 1000 i.u. per 100 g. of sardine, is the richest, and probably the most widely consumed, though herring (850 i.u. per 100 g.) and mackerel (700 i.u.) and various other fatty fish, either fresh or canned, are also commonly consumed. Cow's milk contains about 1 i.u. per 100 g., butter 60 i.u. and dripping 30 i.u. Apart from these, the only important source is egg (60 i.u. per 100 g.).

Reports of dietary surveys do not usually give information on the intakes of adults. In recent years, however, the data of the National Food Survey, which relate to food at the shopping-basket stage, as opposed to actual consumption, have been analysed in terms of this nutrient; and in 1954 a more detailed analysis gave information on the consumption by households of differing composition. Where the household consisted of two adults under 55 years of age only, the daily vitamin D intake was assessed to be 163 i.u. Of this, over 40 per cent. came from margarine, 23 per cent. from fish, and 15 per cent. from eggs. The diet was reported to contain 3,174 calories daily, and since this is appreciably above most estimates of average adult energy requirements, it may be that not all of it was consumed. Even so, the adult intake of vitamin D is clearly quite high.

OTHER ASPECTS

Owing to limitations of space, much has been omitted in this account. The intake of calcium and phosphorus, for example, which is very relevant to the problems that have been discussed, has barely been mentioned because even the worst diets consumed in Britain today contain considerable amounts. Too little has been said, because too little is known, of the quantitative aspects of the contribution of vitamin D made by sunlight falling

on the skin. Osteomalacia has barely been mentioned because it is unimportant in this country. The therapeutic use of vitamin D in renal rickets and certain other conditions has not been mentioned, and for this the reader is referred to articles by Stanbury (1957) and Snapper and Nathan (1957).

Finally, let us consider the future. In the short term we await with eagerness the effect, if any, of reduced intakes of vitamin D upon the incidence of hypercalcæmia. For the long-term issues, let us refer again to the work of Palm, with which this article began. Ultimately, man in his quest for health and beauty may make his cities light as well as lovely. When this is achieved, shall we, even in our drab, cold climate, be able to dispense with the bulk of the vitamin D which we must take by mouth? In the absence of firm data upon the quantitative aspects of the contribution that can be made by sunlight it is almost impossible to say; the lives of women may need to be changed considerably before the effect of sunlight on their skins becomes sufficient for them to acquire reserves, not only for pregnancy and lactation, but for the child during his early life. But eventually such changes, both in our cities and in the lives of their citizens, must be made because they are desirable; when they have been made the consumption of vitamin D may well cease to be a problem.

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VITAMIN C

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THE investigations which have contributed to our knowledge of the action of the vitamins have revealed that here we are faced, as in the study of all living things, with a complexity of action, hormonal and enzyme, which makes even the investigator pause in wonder and speculation; indeed it establishes unequivocally that the secret of life lies in the physiology of the cell. In this series of articles on vitamins, our attention is particularly directed to the part played by botanists, biochemists, physiologists and clinicians in the elucidation of certain specific factors which control mammalian function. Throughout the ages the vitamin which is the subject of this article has been the unknown cause of broken health, disease and death. Scurvy, one of the ancient diseases, has been known for centuries. That the essential antiscorbutic food factor was contained in green vegetables, fruits and germinating pulses was well known to Elizabethan admirals, naval surgeons and famous explorers; that its development is associated with metabolic processes within plants was unknown until demonstrated by Dame Harriette Chick and her co-workers in 1916.

THE DISCOVERY OF VITAMIN C

Since the days when Kramer (1721) wrote on protective foods and Budd (1841) suggested that chemists should seek for the antiscorbutic factor in natural foods, the path of investigation of this essential accessory food factor has been strewn with hopes, frustrations and failures; indeed, many investigators set the problem aside, regarding it as an impossible task. Two important factors were responsible for failure in detecting the active principle: an unawareness of the instability of the vitamin and the difficulty in controlling the required chemical steps of its production by biological assay. The climax to a long period of intensive research came in 1932 when King and Waugh reported that they could obtain 'regular crystalline preparations', Svirbely and Szent-Györgyi that they could protect animals from scurvy by the daily injection of 1 mg. of crystalline hexuronic acid, and Tilmans, Hirsch and Dick, having obtained a crystalline product, noted the correlation between its reducing action and its antiscorbutic effect. Following upon these important findings came the establishment of the molecular structure of vitamin C and the suggestion, by Szent-Györgyi and Haworth, in 1933, that the vitamin should be named ascorbic acid.

BIOSYNTHESIS OF ASCORBIC ACID

The generally accepted pathway by which D-glucose is transformed into L-ascorbic acid is:—

D-glucose→D-glucuronic acid→L-gulonic acid→L-ascorbic acid.

The experimental proof of this depends upon the fact that γ-lactones of D-glucuronic acid and L-gulonic acid, added to cress seedlings or injected into rats, are transformed into L-ascorbic acid. D-galacturonic-methyl ester and L-galactono-γ-lactone behave in the same manner. To the biochemist it is significant that, as King and his colleagues have shown in the rat, D-glucose labelled with C^{14} at position 1 ultimately becomes L-ascorbic acid with C^{14} at position 6. The enzymic conversion of L-galactono-γ-lactone to L-ascorbic acid by plant mitochondria has been fully demonstrated by Mapson (1953), and it has further been shown that mitochondria from the rat liver will catalyse the transformation of both L-gulono- and L-galactono-γ-lactone to L-ascorbic acid. Burns and Evans (1956) have shown in the rat that carboxyl-labelled D-glucuronolactone and L-gulonolactone are converted to carboxyl-labelled L-ascorbic acid; that similarly labelled D-glucuronic acid and L-gulonic acid are not, indicates the importance of the lactone structure in the biosynthesis of vitamin C. Labelled lactones are not converted to ascorbic acid in the guinea-pig (Burns *et al.*, 1956).

Various studies on the enzymatic synthesis of L-ascorbic acid from D-glucuronic acid in animal tissues indicate that, in the liver of animals requiring no dietary ascorbic acid, three enzyme systems are required for this conversion. This occurs only in the kidney in the chicken, pigeon and turtle. The final reaction of the oxidation product of L-gulonate, namely 3-keto-L-gulonate, does not occur in the liver in man, certain species of monkey and the guinea-pig (Grollman and Lehninger, 1957). The failure to form ascorbic acid is due to a relative metabolic defect; the dietary requirement of these species is not due to an abnormally high rate of catabolism of L-ascorbic acid but to a missing component in one of the enzyme systems. Such investigations indicate the nature of enzymatic reaction pathways involved in the synthesis of ascorbic acid and also show reason for observed differences in species requirements for preformed ascorbic acid in the diet.

Much of a controversial nature has recently appeared concerning the relationship between adrenal dysfunction and deranged corticosteroid metabolism in scorbutic conditions; for example, where in normal guinea-pigs no corticotrophin was found in the serum, considerable amounts were present in acutely scorbutic animals, the excess being markedly reduced upon the administration of ascorbic acid (Clayton *et al.*, 1957). An increase of cholesterol in the blood of rats, guinea-pigs and man can be produced by large doses of ascorbic acid, the probability being that liver cholesterol released under these conditions is related to adrenal hormone function (Booker *et al.*, 1957). Such work indicates a possible relationship between steroid synthesis and ascorbic-acid metabolism, and studies on glucose and phosphatase activity in the liver and A.T.P.-ase activity in skeletal and cardiac muscle emphasize the importance of ascorbic acid in terms of carbohydrate metabolism, adrenal activity and protein deficiency.

MODE OF ACTION OF VITAMIN C

Our knowledge of the biological activity of vitamin C in so far as specific coenzyme systems are concerned is very imperfect.

The formula of ascorbic acid shows that it is a derivative of a hexose, namely, L-gulose. The naturally occurring acid is the L-type and is more active than the D-ascorbic acid. The first stage in its oxidation is the production of dehydroascorbic acid which, biologically equivalent to ascorbic acid, is readily reduced to ascorbic acid in the tissues. It is known that dehydroascorbic acid is readily oxidized irreversibly in the presence of copper salts or by heat to products which have no antiscorbutic activity. It is upon the reduction action of ascorbic acid on di-chloro-

phenol-indophenol that the characteristic dye test depends. One of the known biological activities of ascorbic acid is that it can catalyse the oxidation of tyrosine.

Abnormalities occasioned by a deficiency of vitamin C in the mammalian body are due to a failure in the action of the vitamin in the formation of collagen and the biological activity of formative cells (osteoblasts, odontoblasts, ameloblasts). Great stress has been laid upon the effect of the vitamin on the formation of collagen, present in the white fibres of areolar tissue. These fibres, held together by mucin, form the basis of the ground-substance in which the cells of the tissue lie. The study of the part played by the intercellular substance in growth and tissue repair has proved to be of considerable value, not only in the elucidation of collagen disease, but in the mode of action of vitamin C.

Wolbach (1953) and co-workers, having studied both costal cartilage and the rapidly growing epiphysial cartilage of the long bones, concluded that 'scurvy was characterized by an inability of the supporting tissues to produce and maintain intercellular substances'. Epiphysial cartilage plates of long bones in young guinea-pigs, being avascular, offer excellent material for the study of changes in the cell and of matrix formation in ascorbic-acid deficiency. In rapidly growing scorbutic guinea-pigs, the cartilage cells cease to form matrix, become quite irregular in shape and show staining reactions which definitely distinguish them from the normal. Studies on the resorption of bone in cases of scurvy show that the changes which take place do so while the mechanism for calcification, dependent upon adequate vitamin D supplies, is still undisturbed.

There have been several interesting reports on the role of ascorbic acid in collagen synthesis. Mitoma and Smith (1957) have noted that fibroblasts of subcutaneously implanted polyvinyl sponges catalyse the conversion *in vitro* of C^{14}-labelled L-proline to collagen containing hydroxyproline. This is in agreement with the conclusion that hydroxyproline generated from proline is used in protein synthesis.

These studies, of both experimental and human scurvy, strengthen the idea that a complete ascorbic-acid deficiency is characterized by a failure in intercellular material to form connective tissue, bone, cartilage and dentine. Not only are these changes to be found in bones and teeth, but also in ligaments and joints, the attachment of tendons and during absorption of blood clots. The essential basis of growth therefore is the production of a normal matrix in which the formative cells may exercise their physiological functions. It has been suggested by Penney and Balfour (1949) that the intercellular substance associated with fibroblasts in the repair of scurvy is of the nature of a mucopolysaccharide, a finding which has an important bearing upon the possible synthesis of collagen. Collagen exhibits the phenomenon of metachromasia, i.e. basic blue dyes (e.g. toluidine blue) stain collagen pink or red. This occurs in embryonic connective tissue and in the ground-substance in certain stages of wound healing. It is clear that in bone morphological changes are due to alterations in the osteoblasts, whilst in teeth they are due to changes in the odontoblasts; in both cases the formative cells become irregular, degenerate and may eventually disappear. The administration of vitamin C quickly restores the function of the remaining cells, leading generally to excellent recovery. That vitamin C

plays an important part in cell physiology is shown by the work of King (1950) who has demonstrated the lack of phosphatase, esterase and oxidase enzyme in scorbutic tissue, the reduced capacity of the cell to metabolize the amino-acids, tyrosine and phenylalanine, and the diminished activity of many specific oxidative and hydrolytic enzymes.

THE STAGES IN NORMAL REPAIR

The work of Dunphy *et al.* (1956) has shown the chemical changes associated with wound healing in normal, protein-depleted rats and scorbutic guinea-pigs.

On the fourth day following wounds in normal animals histochemical tests reveal large numbers of immature fibroblasts invading the fibrin clot. Intercellular substance is well formed and stains metachromatically with toluidine blue, as also with the Schiff stain and colloidal iron. The relationship between the mucopolysaccharides, such as hexosamine, and collagen, and the latter's relation to tensile strength of the wound have been clearly indicated. In the *normal* animal (white rat), before wounding, the hexosamine (mucopolysaccharides) content of the tissue is approximately 450 mg./100 g. dry tissue, that of collagen about 5 per cent.; on the third day after wounding, the hexosamine is 950 mg./100 g. and on the seventh day an inverse relationship between hexosamine concentration and collagen formation appears. From the third day hexosamine falls steadily to reach the normal figure about the ninth day; in contrast to this, the collagen, at 5 per cent. on the third day, mounts rapidly to approximately 25 per cent. on the ninth day and 30 per cent. on the fifteenth day. The curve of tensile strength follows closely that of the collagen content. These investigators maintain that tensile strength is probably a function of collagen formation rather than merely one of fibroblastic proliferation.

In the case of *protein-depleted* animals the picture is entirely different. The hexosamine content rises to about 700 mg./100 g. on the third day after wounding, remains constant to the ninth day and thereafter falls steadily. The collagen content, at about 5 per cent. on the third day, rises to 15 per cent. on the ninth day, and is maintained at that level for three days. In *scorbutic animals* (guinea-pigs) on a scorbutogenic diet for twenty days before wounding, the hexosamine content of the tissue rises to 600 mg./100 g. dry tissue on the fourth day, then rapidly to 1,350 mg./100 g. on the twelfth day and thereafter falls. The collagen content, initially at about 5 per cent., rises very slowly, not reaching 10 per cent. on the sixteenth day of the experiment. When ascorbic acid was given to such animals in doses of 25 mg./day starting on the eighth day after wounding, the hexosamine content of the tissue fell rapidly while the collagen content rose equally rapidly, restoring the normal pattern of wound healing. This demonstrates the lack of collagen formation in the vitamin-C-deficient animal.

Interesting observations were the rapidity with which the alteration in hexosamine and collagen (hydroxyproline) concentration followed the daily intramuscular injection of 25 mg. of ascorbic acid to the vitamin-C-deficient animals and the restorative effect of methionine added to the diet of the protein-deficient animals. These observations, as the authors state, provide a new perspective of wound healing. They suggest that in *protein deficiency* there is a lack of 'building blocks' of repair, whereas in the *scorbutic animal* the basic materials are present in adequate amounts but cannot be utilized until ascorbic acid is provided. This idea is supported by the histochemical and chemical studies of Gersch and Catchpole (1949), Bradfield and Kodicek (1951) and Persson (1953), which show that in scurvy the mucopolysaccharides in the ground-substance must be abnormal since there is no lack of them. In their studies on skin regeneration in normal and scorbutic

animals, Gould and Woessner (1957) concluded that an impaired hydroxyproline formation may be one of the earliest signs of ascorbic-acid deficiency. The conclusion drawn from these experiments is that 'the rapid production of hydroxyproline in scorbutic animals after the administration of ascorbic acid may be due to the conversion of an accumulated pool of protein rich in proline and glycine to a more immediate collagen precursor rich in hydroxyproline' (Coon and Robinson, 1958).

In a recent report Hill and Bourne (1958) have described histochemical techniques for the study of enzymes, sulphydryl groups, polysaccharides and the use of autoradiography in determining the sites of variation in uptake of the radioactive isotope S^{35}.

When injected or administered by mouth as $Na_2S^{35}O_4$, the isotope is retained as ester-bound sulphate, the most striking and consistent difference between normal and scorbutic guinea-pigs being a decrease in the scorbutic animal in the uptake of S^{35} in the cartilage of some structures, in particular the costochondral junction. That S^{35} is chiefly incorporated in the chondroitin sulphate of costal cartilage has been demonstrated by biochemical methods and the marked reduction in its uptake in scurvy has been shown by several workers (Friberg and Ringertz, 1954; Reddi and Nörstrom, 1954).

This observation is of significance because in scurvy the synthesis of ground-substance by certain cells is believed to be inhibited, perhaps with the formation of abnormal products that cannot be converted into normal intercellular material. It may be that the cartilage cells in those regions, having taken up some labelled sulphate, are unable to use it for synthesis of the normal intercellular material, chondroitin sulphate (Hill and Bourne, 1958).

PLASMA PROTEINS IN SCURVY

A certain amount of discussion centres around the subject of the concentration and nature of the plasma proteins in vitamin-C deficiency. In acute scurvy there is a decrease in albumin (25 per cent.), an increase in α-globulin (10 per cent.) and fibrinogen (50 per cent.) and a decrease in the albumin: globulin ratio. In chronic scurvy albumin may be decreased (15 per cent.), fibrinogen increased (70 per cent.), γ-globulin increased (40 per cent.) but with no change in the α-globulin. It should be noted that a decrease in albumin associated with an increase in α-globulin is not specific, being found in such unrelated diseases as nephritis, diabetes mellitus, rheumatic fever and acute and chronic infections (Howard, 1958).

SIGNS OF DEFICIENCY AND REQUIREMENTS OF VITAMIN C

The first attempt to determine the minimal dose of vitamin C to prevent scurvy and correlate laboratory findings with clinical signs and symptoms was undertaken by the vitamin C subcommittee of the Medical Research Council (1944-46). A full account of the findings of the experiments is given by Bartley *et al.* (1953). The method adopted was to maintain 20 volunteers for six weeks on a diet containing 70 mg. of vitamin C daily. Thereafter they were divided into three groups: ten with no supplement,

seven with 10 mg. daily as a prophylactic measure and three as controls on 70 mg. daily. The clinical examinations included chemical analysis of blood and urine, hæmatological tests, capillary fragility tests, radiography, electrocardiography, tests for fatigue and a study of experimental wounds. In the ten subjects receiving no supplement the first signs, appearing after seventeen weeks, were enlargement and keratosis of the hair follicles on the upper arms, back, thighs, calves and shins, all being associated with hæmorrhages. The initial change was the plugging of the hair follicle by a horny material which held the hair in the follicle; after twenty-six weeks swelling and hæmorrhage of the gums appeared. After thirty-two weeks five of the ten subjects showed exacerbation of acne, not previously recognized as a sign of scurvy. During the period of deprivation there were no significant changes in body weight, in the incidence of infection, or the appearance of the capillaries of the nail bed and conjunctiva; hæmoglobin concentration, red cell, differential, leucocyte and platelet counts and bleeding time remained normal; dark adaptation was not affected and there were no complaints of pain or weakness. Single clinical signs of scurvy, it was concluded, cannot be regarded as specific; deficiency in vitamin C may be only one of a variety of causes responsible for such clinical signs. The appearance and disappearance of the skin changes reflected the intake of vitamin C, indicating that they were but the early stages of the typical hæmorrhagic spots of scurvy. Here also the typical gum lesions always appeared after the skin lesions.

In the seven volunteers who received a supplement of 10 mg. of vitamin C daily no abnormalities appeared before the first 160 days of the experimental period; indeed in most of them no abnormalities appeared for at least 264 days. The dose of 10 mg. of vitamin C daily gave almost complete protection from clinical scurvy, but one must note the conditions under which these experiments were carried out. The volunteers taking 70 mg. daily showed no deficiencies. It is noteworthy that many of the classical signs of scurvy, such as dryness of the skin, night blindness and anæmia, were not observed.

With regard to the curative dosage of vitamin C, volunteers on a scorbutogenic diet with unequivocal signs of scurvy (multiple skin hæmorrhages and gum lesions) showed quick response to a daily dose of 10 mg. Within a week the hæmorrhages into the perifollicular region ceased and within two weeks older hæmorrhages began to lose their purple colour and gradually faded. Within a month the hair follicles with embedded hair had returned to normal, the plug having been discharged, and in most cases the skin had returned to its normal appearance within seven to nine weeks. It would not be justifiable to conclude from these results that 10 mg. a day is sufficient to prevent scurvy. The potential scorbutic status of an individual cannot be assessed by clinical signs alone. It is necessary to know the relation between clinical signs and the vitamin C content of blood plasma and white blood cells.

In the figures now given for the vitamin C content of plasma and white blood cells the method of assessment was the dye-titrating method of Butler and Cushman (1940). The average plasma value for subjects on a 70-mg. dose of vitamin C daily was 0.55 mg./100 ml. plasma. Where there was no supplement at all of vitamin C the average value after thirty-seven days was 0.03 mg., the range being 0.01 to 0.05 mg./100 ml. With regard to the white-cell content, the normal average was 15.6 mg./100 g.; in the totally deprived group it fell to 1 mg./100 g. in 113 days, and remained below this value throughout the period of the experiment. In subjects receiving 10 mg. of vitamin C daily, and this is worthy of note, the white-cell content after a hundred days remained at approximately 2 mg./100 g., the range being 1.5 to 3 mg./100 g.

It is to be noted that about a hundred days elapse between the virtual disappearance of vitamin C from the plasma and the first clinical signs of scurvy but, on the other hand, the concentration of vitamin C in the white cells reached its lowest value three to six weeks before the appearance of these signs. From these results it can be concluded that an intake of not more than 20 mg. of vitamin C daily maintains the plasma level at a variable figure below 0.1 mg./100 ml. An intake of 50 mg. is required before the average vitamin C content of the plasma reaches 0.38 mg./100 ml., which is in contrast to the amount of vitamin C in the plasma, 0.55 mg./100 ml., when 70 mg. of vitamin C are taken per day. The determination of the vitamin C content of white cells is certainly of greater diagnostic value than its estimation in the blood plasma.

From such facts the assessment of vitamin C requirements may be stated. Whilst a supplement of 10 mg. daily cured clinical scurvy in most cases and protected the subjects throughout a period of 424 days, it may be accepted that such a dose could be regarded as the minimum for protection; but the minimum protective doses cannot be accepted without knowing something about age, activity and the general conditions under which individuals live. The League of Nations Health Organization, Technical Commission on Nutrition (1938) accepted 30 mg. of vitamin C daily as the amount which would satisfy all physiological needs. The National Research Council (U.S.A.) Food and Nutritional Board (1943) recommended 75 mg. but 'so long as there is no evidence to support the view that an intake of more than 30 mg. daily has beneficial effects, there is no basis for recommending an intake greater than that amount' (Krebs, 1953).

DIETARY SOURCES OF VITAMIN C

The chief sources of the vitamin are fruits, vegetables and potatoes. Apples, pears, peaches, bananas, grapes contain 3 to 10 mg./100 g.; tomatoes 15 mg./100 g.; oranges, lemons, grapefruit, strawberries 14 to 18 mg./100 g.; blackcurrants 140 mg./100 g.; rose hips 500 mg./100 g.; cabbage, spinach, asparagus 30 to 90 mg./100 g.; raw vegetables, carrots, onions, lettuce, beet, salsify 5 to 15 mg./100 g. The concentration of ascorbic acid in plants depends upon several factors: genetic, manuring, exposure to light, degree of ripeness, time of harvesting and conditions of storage. On storing at room temperature the vitamin is rapidly lost in vegetables,

whereas fruits may retain their vitamin C content well. Old potatoes, particularly if stored for a long time, suffer a loss of anything up to 80 per cent. Methods of preparation of food play a definite part in determining their content of vitamin C; boiling green vegetables may cause loss both by extraction in water and by oxidation under the influence of oxidases. It is important therefore to cook vegetables in a minimal amount of water, bringing them to the boil as quickly as possible. Canning, drying and freezing do not occasion any great loss. Sterilization and storage in cans cause little destruction, largely due to the fact that factories must use freshly picked material.

Foods of animal origin, e.g. eggs, cheese, fats, edible oils, contain no vitamin C; meat and milk about 2 mg./100 g.; liver and kidney 25 and 14 mg./100 g., respectively. Boiling or pasteurization of cow's milk leads to a reduction to about 1 to 15 mg./100 ml. ascorbic acid. This should be borne in mind in the feeding of babies. A baby receiving 500 ml. of pasteurized milk would obtain about 7 mg. of vitamin C. This is enough to protect against scurvy. Breast-fed babies would generally get more vitamin C since the content of vitamin C in human milk depends upon the diet of the mother, and the diet of the mother must be watched carefully because the vitamin C content of food varies greatly with the seasons.

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ANEURINE

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ANEURINE is the official name in the *British Pharmacopœia* for vitamin B_1. It is now usually known to nutritionists as thiamine, since this has been agreed by an international committee on nomenclature.

ACTION

Aneurine is concerned in the metabolism of carbohydrate. It forms part of a coenzyme needed for the further oxidation of pyruvate, which is an intermediate product in the oxidation of glucose. Animals deficient in aneurine show an accumulation of pyruvic acid in the blood, and the tissues from such animals, examined *in vitro*, are found to be unable to oxidize pyruvic acid.

REQUIREMENTS

The requirements of aneurine vary with age and with caloric intake, or more strictly with the intake of carbohydrate. They are increased also in pregnancy and lactation. The nutrition committee of the British Medical Association gives the daily requirements for children as 0.4 mg. at the age of one, rising to 1.1 mg. at the age of eleven. The daily requirement for adults with a caloric intake of 2,250 is 0.9 mg., and with a caloric intake of 4,250, 1.7 mg.

It is possible that the requirements are also increased whenever there is an increased metabolic rate, as in thyrotoxicosis or in fever.

SOURCES

Aneurine is very widely distributed. Unlike the fat-soluble vitamins such as vitamin D, there are few foods which contain no aneurine, and there are few which contain vast amounts. There is little or no aneurine in sugar, whether white or brown, or in the syrups or treacles of varying degrees of refining. There is also little or none in highly refined starchy foods such as polished rice, semolina, tapioca or highly milled wheat flour. White bread in Britain is now fortified with aneurine (and other nutrients) so that it contains about as much as the national bread which was available during, and for some time after, rationing.

Reasonable sources of aneurine include meat, most fish, eggs, bread, potatoes and peas and beans. Some of these foods, like potatoes, do not necessarily contain a high concentration of the vitamin, but provide it by virtue of the amounts of the foods normally consumed. The richest sources are pork, yeast and the germ of cereals: e.g. wheat germ. Extracts of yeast are uncertain sources since the vitamin tends to disappear on storage.

In Great Britain, the chief sources of aneurine in the average diet are bread and cereals, which supply 33 per cent. of the total intake, meat which supplies 23 per cent., and potatoes which supply 16 per cent. Owing to the wide distribution of the vitamin, and to the fortification of bread, a dietary deficiency of aneurine is most unlikely in this country.

DOSAGE

The B.P. doses of aneurine (as the hydrochloride) are given as 1 to 3 mg. daily (prophylactic) and 10 to 30 mg. daily (therapeutic). These official recommendations call for two comments. In the first place, apart from the treatment of acute beri-beri in which, for example, the patient shows rapidly increasing heart failure, it is usually unnecessary to give aneurine as such. It is better to give foods known to be rich in the vitamin, since these will contain other nutrients some of which will undoubtedly be lacking in the patient. Secondly, in so far as recovery is possible, it will occur just as rapidly on doses much lower than ten times the prophylactic level. It is, of course, true that usually no harm is done with quite large doses, but it is misleading to imply that cures require very much more than the prophylactic dose.

SYMPTOMS AND SIGNS OF DEFICIENCY

As with most other vitamins, deficiency of aneurine alone is never seen in man, although it can, of course, be demonstrated in laboratory animals. It is generally accepted, however, that beri-beri is caused chiefly by deficiency of aneurine. The disease takes an appreciably different form in infants and in adults.

Infantile beri-beri.—This is seen almost exclusively in the Far East, although rarely it has been reported to occur in Western countries. It is seen in the first few months of life, and progresses very rapidly. An apparently healthy infant may develop the disease and die within one or two days. The first signs are loss of appetite, restlessness, vomiting and colicky abdominal pain, which is accompanied by paroxysms of screaming. Later, there are œdema, tachycardia, dyspnœa and aphonia due to œdema of the larynx. The latter is responsible for the characteristic beri-beri 'cry'. Heart failure soon ensues, and an increased intracranial pressure which leads to twitchings, coma and death.

Adult beri-beri.—In older persons, beri-beri is a chronic disease. In the early stages, it shows itself in a variety of vague, unspecific symptoms of insidious onset and with few or little signs. The patient feels generally unwell, has a poor appetite, and may complain of nausea, abdominal discomfort and constipation. Weakness of the limbs, with numbness and tingling, are common. Examination may reveal nothing abnormal in these early stages. Later, there may be tachycardia, with impairment of the tendon reflexes, and perhaps a little gravitational œdema. Still later, there are distinct neurological signs taking the form of an ascending polyneuritis.

That is, the effects are chiefly in the limbs, showing most commonly as wrist-drop and ankle-drop. The latter gives rise to a 'stepping' gait. In some patients, œdema is not seen (dry beri-beri). In others, it is a major feature of the disease (wet beri-beri). In wet beri-beri, signs of heart failure may develop, with dyspnœa, palpitation and precordial pain. The condition often deteriorates suddenly, and death may occur quickly. Apart from this, the disease is generally chronic and long standing; when this is so, there may be lesions of the optic nerve leading to scotomas and, rarely, to complete blindness. Dry beri-beri usually progresses until the patient is bedridden and death may then occur through intercurrent infection.

The diagnosis of beri-beri is especially difficult in the early stages. The signs and symptoms are found in other nutritional deficiencies, and in a wide range of non-nutritional conditions. As with all deficiency disease, the diagnosis of beri-beri should not be made unless there is evidence either of primary deficiency—that is, a deficient diet—or of secondary deficiency —that is, increased requirement or reduced absorption. Classically, beri-beri is found endemically in countries where polished rice is the main food and where other foods are poorly represented, but it can also occur sporadically in other countries, where an individual is found to live largely on highly milled cereal or other starchy foods low in the vitamin.

Secondary deficiency is sometimes seen in pernicious vomiting of pregnancy. The polyneuritis of alcohol may also sometimes be a secondary deficiency of aneurine; this occurs as a combination of a low intake of foods containing aneurine, and defective absorption due to alcoholic gastro-enteritis. Again, deficiency may occur in persons with a marginal intake who are engaged in heavy physical work in which the requirements are increased. Cases of this sort are sometimes found to occur seasonally, with a seasonal variation in the patient's work.

As suggested earlier, patients with beri-beri are likely to be suffering from deficiencies of other nutrients, as well as of aneurine. The vitamin is found with other members of the B group of vitamins in the germ of cereals and in animal foods rich in protein, so that a diet which produces beri-beri tends to produce deficiency also of protein, riboflavine and nicotinic acid. Occasionally, beri-beri is associated with a deficiency of vitamin C (Rand scurvy) or of vitamin A. The signs of these deficiencies which are most commonly seen in beri-beri are scrotal dermatosis, cheilosis, angular stomatitis and a raw red tongue. It is, then, important to remember that beri-beri, like most nutritional deficiency diseases, requires multiple nutritional therapy, and that this can best be given by vitamin-rich foods. Since we have not yet achieved the identification of all the existing nutrients, such foods will be more likely to make good dietary deficiencies than multiple mixtures of isolated vitamins, however complex these may be.

Wernicke's encephalopathy.—This condition is usually associated with chronic malnutrition. Occasionally, this is due to an inadequate diet. More often, the condition is secondary to alcoholism, chronic gastro-intestinal dis-

orders, or pernicious vomiting of pregnancy. The clinical features are nystagmus, ophthalmoplegia, ataxia and mental confusion. Most if not all of these effects can be reversed by the administration of aneurine.

TREATMENT AND PROGNOSIS OF ANEURINE DEFICIENCY

Prevention of endemic beri-beri, in countries such as India, China, the Philippines and Malaya, is entirely a matter of improved nutrition. Where rice is the staple food, and provides up to 90 per cent. of the calories, the incidence of the disease has increased greatly in the last one hundred years or so, following the replacement of home-milling by mechanical milling. Beri-beri can be prevented either by increasing the proportion in the diets of such foods as meat, fish and vegetables, or by decreasing the loss of aneurine in the milling of the rice, or by enriching (fortifying) the polished rice with aneurine and perhaps other nutrients. General improvement of the diet is obviously a long-term process of improved food production and food distribution. A return to less highly polished rice is always resisted by a population no longer accustomed to it. An alternative is parboiling in which the rice is partially cooked before milling. In this way, some part of the vitamins is transferred into the inner part of the rice kernel, and remains there after milling. Enriching has proved highly successful in the Philippines, and has resulted in a tremendous fall in the incidence of, and mortality from, beri-beri.

In beri-beri, the heart failure and œdema clear up amazingly rapidly with the administration of aneurine. It is usually quite effective by mouth, in the form of aneurine-rich foods, or as the pure vitamin alone or with other vitamins. Parenteral administration may be necessary when heart failure is a serious threat to the life of the patient, but, even with oral administration, the patient will have recovered dramatically within a few hours. The œdema also improves rapidly in a day or two, although some residual œdema may be seen for a week or more. Many of the neurological symptoms also clear up fairly rapidly. Paræsthesiæ and weakness will improve within days. If, however, there is long-standing paralysis, or optic atrophy, improvement is slow and may never be complete. It is worth persisting in the administration of the vitamin for many months.

THE USE OF ANEURINE IN THE TREATMENT OF OTHER DISEASES

There are many conditions for which aneurine is prescribed. These may be divided into those in which it is supposed that there is deficiency of the vitamin, and other quite unrelated conditions in which empirically it has been suggested that aneurine has a therapeutic effect.

Diseases alleged to be due to vitamin deficiency.—Because of the multiplicity of signs and symptoms seen in beri-beri, and in experimental animals with deficiency of aneurine, a variety of conditions with similar signs and symptoms is constantly being treated with aneurine. The sort of reasoning

seems to be that, if a patient has symptoms at all similar to those found in beri-beri, then they will be cured by the administration of aneurine. Thus, since polyneuritis is a feature of beri-beri, it is suggested that sciatica, trigeminal neuralgia and brachial neuritis can reasonably be expected to show improvement with aneurine. With this sort of false logic, the following conditions amongst others have been treated with aneurine:—

Neurological.—Multiple sclerosis, herpes zoster, diphtheritic polyneuritis, the neuritic symptoms and the cord lesions in pernicious anæmia, a variety of local types of neuritis such as sciatica and brachial neuritis, optic neuritis and tobacco amblyopia, and toxic neuritis due to arsenic, lead and mercury.

Gastro-intestinal.—Anorexia, constipation.

General.—Impaired growth of children.

In a few rare instances, there is undoubted evidence that the dietary requirements of aneurine are not being met; in such cases there are usually other signs and symptoms of deficiency. Only in these cases is aneurine of any use. In the overwhelming majority of cases, there is no evidence whatever that aneurine produces any improvement. It is extraordinary that one still finds instances where aneurine is given, often by injection, to patients with conditions quite certainly not due to deficiency of the vitamin. The most recent case which has come to my attention was an elderly woman suffering from severe low back pain. Only after a prolonged series of injections of large doses of aneurine, with no improvement, was the condition diagnosed as vertebral collapse due to senile osteoporosis.

Other diseases.—From time to time, reports have appeared that aneurine is effective in the treatment of a variety of skin conditions, of mucous and ulcerative colitis, of uterine carcinoma, of morphine addiction, and for the increasing of resistance to fatigue. None of these claims has been substantiated.

TOXICITY

Taken by mouth, aneurine in quite enormous doses is completely without harmful effect. Parenteral administration in animals has shown that toxic effects are produced only with doses of at least one thousand times the daily requirement.

In man, as we have seen, parenteral administration of aneurine is rarely warranted. It has been shown, nevertheless, that up to 500 milligrams are almost always without effect. Very occasionally, patients who have had aneurine parenterally on several successive occasions develop a hypersensitivity. In these rare cases, the effect takes the form of an anaphylactoid reaction. In mild cases, it takes the form of a feeling of burning, urticaria, restlessness, nausea, dyspnœa, and tachycardia. In more severe cases, there may be angioneurotic œdema, pulmonary œdema, hæmorrhage into the gastro-intestinal tract, and collapse. The severity of the reaction is not related to the amount of aneurine injected.

RIBOFLAVINE

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THE history of the isolation and identification of riboflavine illustrates how developments in one branch of biochemistry sometimes lead to new and unexpected advances in another apparently unrelated field.

HISTORY

Riboflavine was first clearly identified through its properties as a part of a respiratory enzyme. The story is an intriguing one. Following the discovery that 'water-soluble vitamin B' consists of at least two components—heat-labile (aneurine) and heat-stable—attempts were made to isolate the hypothetical 'heat-stable vitamin B_2' which was recognized as necessary for the growth and well-being of several species of animals. Kuhn and his colleagues, using the growth of rats as a means of testing for the vitamin, sought to isolate it from milk. Finally in 1933, from over 1000 gallons of whey, they successfully isolated about 1 g. of crystalline riboflavine (Kuhn, Gyorgyi and Wagner-Jauregg, 1933). The striking feature of these crystals was their yellow colour. A year previously, Warburg and Christian (1932) had published their studies on tissue oxidation in which they identified a new respiratory enzyme consisting of a large colourless protein molecule combined with a yellow pigment. Neither component had enzymic properties separately, but only in combination. The inspired guess was that Kuhn's crystalline vitamin might be identical with the pigment in Warburg's yellow enzyme—a guess that proved to be right. Only two years elapsed before the chemical structure of riboflavine had been established and, more remarkable still, its synthesis in the laboratory had been accomplished.

Subsequent research showed that riboflavine did not possess all the biological properties previously attributed to the hypothetical 'vitamin B_2'; other heat-stable components of the vitamin B complex were later identified (e.g. nicotinic acid, pyridoxine) accounting for some of these properties. Nevertheless, the discovery of riboflavine was an important milestone in the development of biochemistry and has led to far-reaching advances in knowledge of cellular metabolism.

Thus riboflavine was first identified as an essential component of an enzyme and not as a vitamin. It is for its enzymic properties that it is still chiefly regarded by biochemists.

ACTION

Riboflavine is probably present in every cell of the human body. It occurs in combination with phosphoric acid to form a flavine nucleotide. This is often

linked with adenylic acid (itself composed of phosphoric acid, ribose and adenine), to form flavine adenine dinucleotide (FAD). FAD can accept hydrogen atoms at the double bonds on two nitrogen atoms in the flavine molecule and is thus converted to reduced FADH. FADH is quickly oxidized again in the presence of cytochrome. Thus FAD is thought to form an essential link in a chain of reversible reduction-oxidation reactions on which tissue respiration normally depends. FAD is essentially a coenzyme and cannot work unless combined with a specific protein to form a flavoprotein. Several different flavoproteins have been described, differing somewhat in the nature of their specific protein and in their enzymic behaviour.

Considering the great importance attached to riboflavine by biochemists, it is remarkable that the clinical features ascribed to its deficiency in man are apparently so trivial. There are several possible explanations for this. First, there may be little destruction of the vitamin within the body; the molecules of riboflavine liberated in the course of the wear-and-tear of tissues may be used over and over again for the synthesis of new flavoproteins. If this is indeed the case, the true dietary 'requirement' of riboflavine would, of course, be very much less than is currently supposed. Secondly, there is an additional possible source of riboflavine, derived from biosynthesis by bacteria in the large intestine. Undoubtedly the bacterial flora of the gut can synthesize riboflavine, since the fæces sometimes contain more of the vitamin than the diet supplies; but whether any of this product of biosynthesis is ordinarily absorbed and made available to the body is a matter of speculation. Lastly, it is possible that the human body has certain limited powers of synthesizing the vitamin for itself, given the necessary dietary raw materials to do so, just as the body can synthesize nicotinic acid provided that the diet contains a sufficient amount of its 'provitamin'—the amino-acid, tryptophan. It is worth remembering that the dietary essentials required by one species of animal are not always needed by another species. Thus the rat can make for itself all the ascorbic acid it needs, but is dependent upon its diet for its supplies of riboflavine. Perhaps we are superior to the rat, at least in this respect, and are not primarily dependent on our diet to keep our cells stocked with FAD.

SIGNS AND SYMPTOMS OF RIBOFLAVINE DEFICIENCY

Corneal vascularization.—In rats deficient in riboflavine, the normally avascular cornea of the eye becomes infiltrated with microscopic capillary blood vessels. Smoky patches appear in the cornea which shows a tendency to ulcerate. There is a possible explanation of this. The interstitial cells of the cornea lacking a blood supply are likely to be particularly dependent on flavoproteins for their oxidative processes. The riboflavine necessary for the synthesis of these flavoproteins is probably derived from the tears which bathe the anterior surface of the cornea, and which, as Philpot and Pirie (1943) have shown, contain considerable amounts of riboflavine.

In man, a vascular cornea akin to that seen in riboflavine-deficient rats,

was described in patients suffering from pellagra in the Southern States of the United States of America (Sydenstricker, Sebrell, Cleckley and Kruse, 1940). This lesion was usually accompanied by lacrimation and photophobia, which made proper examination with a slit lamp difficult. It was often associated with angular stomatitis, cheilosis and other features of the orogenital syndrome. The corneal vascularization and other features persisted, even when the primary pellagrous lesions had been relieved by adequate doses of nicotinic acid, and did not subside till later, when riboflavine had been administered. Professor Sydenstricker twice gave up his practice and university duties, in 1941 and again in 1944, to give all the aid he could to Britain in the 1939-45 War. In the course of his wartime experience in Britain he personally examined with a slit lamp the corneæ of many British wartime workers and reported that corneal vascularization in Britain was rare. When present, it was probably attributable to irritation by dust, smoke, and the like. He found little evidence of riboflavine deficiency in wartime Britain (personal communication).

Angular stomatitis and cheilosis.—Soggy, greyish-white fissures at the corners of the mouth (angular stomatitis), and a red, denuded epithelium at the line of closure of the lips (cheilosis), were formerly a common feature of pellagra in the Southern States of the United States of America. It was reported that they did not respond to treatment with nicotinic acid, but improved once riboflavine was also given. Angular stomatitis and cheilosis are sometimes seen in debilitated patients in Britain, especially if they have ill-fitting dentures, but it now seems clear that they are not a specific sign of riboflavine deficiency, since the response to riboflavine therapy is seldom impressive or convincing.

Orogenital syndrome.—This condition, first described by Stannus in Africa in 1911, includes angular stomatitis, photophobia, lacrimation and, in addition, a scaly, greasy eczema about the face and an itching, erythematous dermatitis around the genitalia. It caused much distress among British prisoners of war in Japanese hands (Smith and Woodruff, 1951). No single vitamin seems to be curative, although it responds well to natural preparations of the entire vitamin B complex, such as yeast extract, wheat germ or rice polishings.

If riboflavine deficiency ever causes illness in man, its effects have not yet been sufficiently defined. A vascular cornea, angular stomatitis and cheilosis cannot be regarded as specific signs of deficiency of this particular vitamin. The diagnosis of 'ariboflavinosis' served a temporary purpose in drawing attention to such clinical signs, but is now best forgotten.

RECOMMENDED ALLOWANCES

As with all other vitamins, it is not possible to define daily 'requirements' in any precise terms; true requirements for riboflavine probably vary very much from one individual to another. It has already been noted that some of the riboflavine in the FAD of the body may come either from internal

metabolic synthesis or from biosynthesis by bacteria in the gut. If this is indeed the case, the requirements of the body for riboflavine may be largely influenced by the intake of other nutrients providing the raw materials from which it can be made. In the present state of knowledge it is impossible to do more than attempt to define a 'recommended allowance', based on estimations of the amount of riboflavine present in the diets of people who are obviously healthy. A well-balanced British diet usually contains between 1 and 2 mg. a day of riboflavine.

The British Medical Association committee on nutrition (1950) sought to relate riboflavine requirements to energy expenditure and recommended 0.6 mg. per 1000 calories as a suitable allowance. The committee admitted that the relation between caloric intake and needs for riboflavine was 'hardly more than suggestive', but this tentative relationship has received recent backing from Bro-Rasmussen (1958). In the United States, by contrast, attempts have been made to relate riboflavine requirements to protein intake and this view has the support of the Food and Nutrition Board (1953).

There seem to be so many uncertainties at the present time about riboflavine requirements that, on the present evidence, it is probably wise to be cautious in attempting to define them with precision. But this should not belittle the importance of riboflavine as a useful nutrient present in all good mixed diets.

SOURCES

The best dietary sources of riboflavine are liver, milk, eggs and green vegetables. Unlike other components of the vitamin B complex, it is present in relatively small amounts in whole-grain cereals. Milk and milk products are good sources, as also are undistilled malted liquors, such as beer and ale. Ordinary cooking methods destroy little of the vitamin, but it may be washed out of vegetables if they are cooked in too much water which is afterwards thrown away. It is also destroyed by sunlight, as when milk bottles are left standing on the doorstep on Sunday mornings.

THERAPEUTIC USES

Dosage.—The dose usually recommended is 10 mg. three times daily by mouth. There seems to be no ordinary advantage in giving it parenterally since it is quickly and easily absorbed from the gut.

Riboflavine is one of those embarrassing vitamins which have been offered to us by the chemical industry before we felt the need for it. In the twenty-five years that have elapsed since its first identification, it has been tried empirically in every imaginable clinical disorder, without any clear-cut benefit. It is included in almost all 'multivitamin' capsules, but what chemical changes it may undergo in propinquity with other potent nutrients in the capsule does not seem to have been reported. So far as I know, there is only one certain use for synthetic riboflavine at the present time: in the treatment of keratomalacia. This disease is still a serious cause of blindness

among children in Ceylon, India and other Eastern countries. It is important to distinguish it from xerophthalmia, which is a chronic affection of the scleral conjunctiva and afflicts many thousands of adults in the East, although usually without serious loss of vision. Keratomalacia, on the other hand, is a desperate disease of small children raised on a diet devoid of milk and other sources of riboflavine. The avascular collagen tissue of the cornea breaks down, possibly through lack of FAD to support the metabolism of its interstitial cells. Riboflavine, 5 mg. thrice daily by mouth, in addition to cod-liver oil may be a useful adjunct in the treatment of keratomalacia.

Toxic effects.—So far, there appear to be no reports of any toxic effects arising from an excessive dose of riboflavine. The explanation is probably that riboflavine, like other water-soluble vitamins, has no renal threshold and is quickly excreted in the urine if taken in excess—in contrast to the fat-soluble vitamins which can accumulate in the body, producing toxic manifestations.

SUMMARY AND CONCLUSION

There can be no doubt that riboflavine has a precise enzymic role in the respiratory mechanisms of normal human tissues. The vitamin is supplied in largest amounts by diets that include plenty of dairy produce and green vegetables. There is no certainty, however, about true dietary requirements for riboflavine in healthy adults. Requirements during childhood and in various chronic diseases cannot be defined except by conjecture. Attempts have been made in the past to identify certain clinical signs as specific indications of riboflavine deficiency and to dignify them with the diagnosis of 'ariboflavinosis'; but this, like the sign of Jonas the prophet, is best forgotten. There are no precise indications for prescribing riboflavine in present-day British practice, either for prophylactic or therapeutic purposes.

The spelling of riboflavine in this article conforms with that in the *British Pharmacopœia* 1958. In most journals of nutrition it is now spelt 'riboflavin'.

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NICOTINIC ACID

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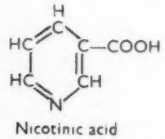
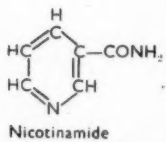
NICOTINIC acid is now well established as an important member of the water-soluble vitamin B group. It was first discovered in 1867 as an oxidative product of nicotine and in 1911 was isolated by Funk from such natural sources as yeast and rice polishings. He tentatively suggested that it might be the anti-beri-beri factor. Following this, little attention was paid to its biological role until 1934 when Warburg and Christian discovered coenzyme II (triphosphopyridine nucleotide, TPN) in human red blood cells. They observed the amide of nicotinic acid, nicotinamide, to be an important constituent of this co-factor. Almost simultaneously, Von Euler announced that it was also present in coenzyme I (diphosphopyridine nucleotide, DPN) which he had isolated from heart muscle. The importance of these compounds in clinical nutrition was realized when Elvehjem reported that nicotinamide was the active principle of liver extracts which cured canine black tongue. He announced this finding in a letter to the *Journal of the American Chemical Society* in which he suggested that a clinical trial be made in the analogous human disease, pellagra (Elvehjem *et al.*, 1937). This was rapidly done and the results were dramatic.

BIOLOGICAL FUNCTION AND BIOSYNTHESIS

The structural formula (fig. 1) demonstrates that nicotinic acid consists of the nitrogen-containing base, pyridine, to which is attached a carboxyl group. Nicotinic acid is rapidly converted in the body to its amide, nicotinamide.



Nicotinic acid



Nicotinamide

FIG. 1.—Structural formulæ of nicotinic acid and nicotinamide.

Nicotinic acid is an essential vitamin because, in the form of nicotinamide, it constitutes an integral part of the two coenzymes, DPN and TPN (fig. 2).

Both of these co-factors are nucleotides and contain nicotinamide, two molecules of ribose (a five carbon sugar), the base adenine, and either two or three phosphate groups.

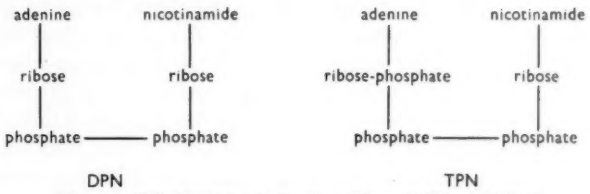


FIG. 2.—Relationship of nicotinamide to DPN and TPN.

The biological function of these enzymes is either to donate or accept hydrogen ions in numerous vital oxidation-reduction reactions. After the nucleotide has been reduced (i.e. has accepted a hydrogen ion) it is often abbreviated as DPNH or TPNH. A typical oxidation-reduction reaction is illustrated in fig. 3.

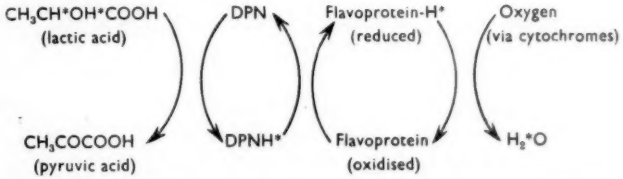


FIG. 3.—A typical oxidation-reduction reaction. Here DPN accepts hydrogen from the substrate (lactic acid) with the resulting formation of DPNH. The loss of hydrogen ion from lactic acid (i.e. oxidation) yields pyruvic acid. The asterisk traces the hydrogen ion from the substrate to its final appearances in water.

The demonstrated conversion of lactic acid to pyruvic acid is typical of many important oxidation-reduction reactions that are involved in the metabolism of carbohydrates, fats and proteins. Some of these reactions require DPN, others TPN. During this passage of hydrogen ions, the important energy-rich compound, adenosine triphosphate (ATP), is synthesized. This process is known as oxidative phosphorylation. It is thus apparent that DPN and TPN play a key role in metabolism.

Biosynthesis.—Although nicotinic acid and nicotinamide are essential metabolites, they do not have to be present in the diet. This seemingly paradoxical situation exists because nicotinic acid can be formed in the body from the amino-acid, tryptophane. The series of reactions by which tryptophane is transformed to nicotinic acid need not be elaborated here except to emphasize that in this conversion three other vitamins are necessary: pyridoxine, riboflavine and aneurine. As would be expected therefore, tryptophane can cure or prevent lesions of nicotinic-acid deficiency, so long

as these other three vitamins are present in sufficient amounts. Another corollary of the presence of this biosynthetic pathway is that nicotinic-acid deficiency may be aggravated by a relative or absolute tryptophane deficiency.

Absorption, distribution and excretion.—Nicotinic acid and nicotinamide are water-soluble and readily absorbed when given by mouth or parenterally. After absorption the vitamin is distributed to all tissues. Since very little of the administered vitamin appears as such in the urine, it is evident that significant metabolism to other derivatives occurs. The chief excretory products consist of methyl derivatives (N-methyl nicotinamide) and, to a lesser extent, of glycine derivatives (nicotinuric acid). There are other complex metabolites excreted, but some of these have not yet been definitely identified.

NUTRITIONAL ASPECTS OF NICOTINIC ACID

Occurrence.—Nicotinic acid occurs in nature as nicotinamide. It is widely distributed throughout all foodstuffs, since TPN and DPN are necessarily present in all cells. Good dietary sources are meat, offal, yeast, whole grain and meat extracts, whilst polished rice, white flour, fruit, vegetables and milk are relatively poor sources. As nicotinamide is heat-stable and light-resistant, very little of it is lost when food is cooked, except by diffusion into cooking water, which may be thrown away.

Requirements.—As with any vitamin, the exact daily requirement is unknown and, indeed, such a concept is meaningless, for the requirement depends upon so many variables such as the nature of the rest of the diet (e.g. its tryptophane content) and the metabolic activity of the body. The requirement increases with stresses such as fever, trauma and heavy manual work. The American Food and Nutrition Board (1948), however, recommends a daily allowance of 12 to 18 mg. for men and 10 to 15 mg. for women. These values are based on animal experiments and on the amount of pellagra-preventing foodstuffs needed to keep a pellagrous patient in remission. The recommendation put forward by the British Medical Association nutrition committee in 1950 was very similar.

NICOTINIC-ACID DEFICIENCY (PELLAGRA)

Causation.—Nicotinic-acid deficiency becomes overt when the metabolic demands of the patient exceed his supply, whether this be derived directly from the diet or from biosynthesis. For convenience the disease is divided into the primary (endemic) variety and the secondary form. Primary pellagra is a manifestation of poverty and ignorance. It is especially prevalent in areas where the underprivileged subsist on maize, as maize protein is very low in tryptophane. Thus, not only the intake of nicotinamide is low but the supply of body needs by biosynthesis is precluded by the tryptophane deficiency. The alternative suggestion that maize contains a pellagra-producing toxin is based on tenuous evidence. Before 1945 the disease was common in the southern states of America where in 1938 there were about

half a million sufferers, of whom 3,500 died. The advent of an enlightened social and nutritional programme has now made this form of the disease a rarity in the United States. In secondary pellagra, which is uncommon, the deficient intake may be due to a variety of causes: e.g. diseases of the mouth or gut which prevent the ingestion or absorption of food, food faddism, alcoholism and ill-balanced therapeutic diets. A full review of secondary pellagra has been given by Bean *et al.* (1944). In both groups there is often a precipitating factor which exposes a latent deficiency by increasing metabolic demands: e.g. surgical trauma, alcoholism, pregnancy, lactation, growth spurt, thyrotoxicosis, infection and increased physical work.

Two special examples of secondary pellagra must also be considered. The first may rarely occur in patients with malignant carcinoid tumours. Normally, about one per cent. of the body's supply of tryptophane is converted to 5-hydroxytryptamine (serotonin). In patients with a carcinoid tumour as much as 60 per cent. of the tryptophane may be diverted along this pathway. In addition, when anorexia, diarrhœa and general weakness impair food intake, the two factors combined may account for the occasional manifestation of pellagra (Bridges *et al.*, 1957). The second and more obscure example is that which may occur during treatment with isoniazid—an analogue of nicotinic acid. The patients reported to have developed this syndrome have all had a poor food intake associated with their primary disease and have responded to nicotinic-acid treatment (Harrison and Feiwgi, 1956).

Clinical picture.—The prodromal manifestations of pellagra are usually prolonged and bizarre. They include loss of weight, ill-defined indigestion, alteration of bowel habits (either constipation or diarrhœa), lassitude, weakness, irritability, headache, insomnia, palpitations, burning sensations, dizziness and flights of ideas. Obviously such a patient may be misdiagnosed as having innumerable unrelated physical conditions or, most likely, neurasthenia. Eventually, the striking manifestations are in the skin, gut and psyche. The typical skin lesions occur mainly on exposed areas and are thought to be related to sunlight. They are symmetrical and sharply demarcated from the surrounding skin and are in a constant state of flux, starting as an area of erythema which passes through a darker brown phase before desquamation occurs. After repeated attacks permanent pigmentation ensues, with thickening of the skin. Variants may be seen. An atypical distribution is usually associated with scars or areas of skin irritation. How much of the skin lesion is modified by dirt in the endemic patient is difficult to assess. Sometimes there are no obvious skin lesions. The mucous membranes have red sodden lesions. In the mouth a secondary Vincent's organism infection occurs, and vaginal discharges are common. Anorexia, abdominal distension and diarrhœa become pronounced. Profound mental disturbances may ensue with dementia and hallucinations. Each patient's symptoms are different, but if a relapse occurs the same pattern usually repeats itself.

Biochemical findings.—The laboratory gives little help in the diagnosis of pellagra. Blood levels of nicotinamide, DPN and TPN tend to be low in deficient patients, but the overlap of values between a normal and deficient group of persons is so great that such measurements are of little practical value in the individual case. Tests measuring urinary excretions of nicotinic acid and its derivatives, with or without previous nicotinic acid loading, are likewise disappointing.

Treatment.—Although patients with pellagra will usually have other deficiencies besides that of nicotinamide, treatment with nicotinamide will nevertheless bring about rapid improvement in acute skin and mucosal manifestation, with clearing of the oral infection, improvement in the mental status, relief of gastro-intestinal symptoms and increase in the patient's strength. Treatment should be aimed at giving an adequate mixed diet with nicotinamide supplements which should be given frequently: e.g. 50 mg. ten times daily. If the patient is very ill and vomiting, intravenous nicotinamide, 300 mg. a day in glucose, may be given and other vitamin supplements added. As has already been indicated, under certain conditions large doses of tryptophane may also be effective. Precipitating factors causing an increased demand must be sought for and corrected when possible.

PHARMACOLOGY AND OTHER USES

Nicotinic acid has a direct vasodilator action on blood vessels which in man is felt as a flush especially of the face. This may last for hours. The effect is not shared by nicotinamide so that the latter preparation is preferred when correcting a deficiency. The vasodilator effect has little practical therapeutic usefulness except possibly as a dramatic placebo.

Recently various workers have reported the sustained lowering of serum cholesterol levels in patients taking large doses (3 to 6 g.) of nicotinic acid (Altschul *et al.*, 1955; Parsons and Flum, 1957). In the experimental animal this is associated with an increased production and turnover of cholesterol. These observations were made with a view to treating patients with atheroma but, as the role of blood lipids in the genesis of atheroma and its complications is highly debatable, the results of this treatment must be evaluated with the utmost caution.

Nicotinic acid has not been exempt from the abuse afforded other vitamins. Ill-advised claims for its potency in a variety of ailments and situations have not been substantiated.

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PYRIDOXINE (VITAMIN B6)

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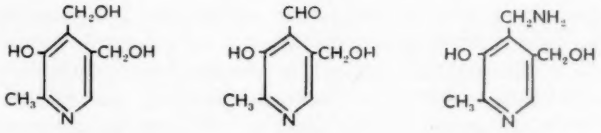
In 1934, György first demonstrated the existence of a substance distinct from the water-soluble food factors known at that time, lack of which produced dermatitis in experimental animals. This substance was called vitamin B_6. Four years later a crystalline compound capable of curing vitamin B_6 deficiency symptoms was isolated almost simultaneously in a number of different laboratories and, as it was a pyridine derivative, the name pyridoxine was adopted for it. Thus, vitamin B_6 and pyridoxine became synonymous terms. Later, however, it was shown that the therapeutic effects of vitamin B_6 could be produced by at least two other naturally occurring substances, pyridoxal and pyridoxamine (fig. 1), and the term vitamin B_6 is now more correctly applied to this group of substances.



PYRIDOXINE PYRIDOXAL PYRIDOXAMINE

Fig. 1.—Structural formulæ of pyridoxine, pyridoxal and pyridoxamine.

MODE OF ACTION

Pyridoxine exerts its effects mainly by acting as a coenzyme in the decarboxylation and transamination of a number of amino-acids. This accounts for the increased requirement of the vitamin which has been observed to follow the administration of high-protein diets. Pyridoxine deficiency decreases transaminase activity and shunts greater amounts of amino-acids into other metabolic processes, such as deamination. The increased production of urea which occurs in vitamin B_6 deficiency states may be explained on this basis. In addition, pyridoxine plays an important part in the metabolism of tryptophane, serine, cysteine and threonine. Normally, tryptophane is converted in the body into kynurenine, and vitamin B_6 is essential for the breakdown of this into alanine and anthranilic acid. If this cleavage cannot take place kynurenine accumulates and is converted into xanthurenic acid which is then excreted in the urine in abnormal amounts. Determination of the urinary xanthurenic acid level thus forms a useful test for vitamin B_6 deficiency. It also appears to be necessary for normal adrenocortical function, and forms an essential part of the enzyme system responsible for the interconversion of certain fatty acids.

Several substances closely related chemically to pyridoxine act as vitamin B_6 antagonists, and these so-called antimetabolites, the most potent of which is desoxypyridoxine, have been used to study the effects of deficiency in man.

SYMPTOMS AND SIGNS OF DEFICIENCY

Vitamin B_6 deficiency due to malnutrition rarely if ever occurs alone, for diets deficient in this vitamin are generally also deficient in others of the B group. Thus, our knowledge of the symptoms and signs of pure vitamin B_6 deficiency in man is based on observations following the administration of the antimetabolite, desoxypyridoxine, to patients already receiving a diet devoid of vitamin B_6. Hawkings and Barsky (1948) showed that adults receiving a pyridoxine-deficient diet alone for periods of up to two months remained more or less symptom free. Vilter *et al.* (1953), however, were able to produce marked symptoms and signs of deficiency by concurrently administering desoxypyridoxine. Within two to three weeks, seborrhœa-like skin lesions occurred around the eyes, nose and mouth, together with cheilosis, glossitis, weakness, dizziness and vomiting. There was also a mild lymphocytopenia. These did not respond to treatment with riboflavine, nicotinamide or aneurine but disappeared within three days of administering pyridoxine. The ratio between the amount of pyridoxine necessary to remedy the deficiency and the desoxypyridoxine was approximately 1:1.

The skin lesions produced by vitamin B_6 deficiency are characterized by atrophy of the epidermis, the hair follicles and the sebaceous glands, with loose hyperkeratosis and loss of subcutaneous fat. Peripheral neuritis may also occur, and the neuritis which often develops when large doses of isoniazid are used in the treatment of tuberculosis may be a manifestation of vitamin B_6 deficiency. Pyridoxal and isoniazid readily form a hydrazone which is metabolically inactive and is rapidly excreted in the urine.

Young infants appear to be more susceptible to vitamin B_6 deficiency than older children or adults. After one to two months on a deficient diet a gradual failure to gain weight occurs and a hypochromic anæmia develops. These respond rapidly and completely to administration of pyridoxine. Irritability and convulsions may also occur, particularly in infants receiving proprietary foods in which the vitamin B_6 has been destroyed by autoclaving, and in one such case electroencephalographic changes which were reversed within three minutes by an intravenous injection of 100 mg. of pyridoxine have been reported.

During vitamin B_6 deficiency, both in adults and infants, pyridoxic acid rapidly disappears from the urine and is replaced by xanthurenic acid produced by abnormal tryptophane metabolism.

DISTRIBUTION OF PYRIDOXINE IN FOOD

Vitamin B_6 is widely distributed in foods. Yeast, liver and cereals are particularly good sources and there is an increase in the content of this vitamin in cereals on germination. Fish is a moderately good source, whilst vege-

tables and milk contain little. In hydrolysed foodstuffs it is present mainly as pyridoxal and pyridoxamine, but in those of fresh plant origin pyridoxine is also present. Because of the importance of milk in infant nutrition the vitamin B_6 content of milk products is of interest. Fresh milk contains about 0.3 mg. per litre and no significant losses occur during drying and storage of dried milk or during pasteurization.

Apples	0.3	Liver (beef)	1.7
Banana	3.2	Marmite	4.0
Beans (dried)	5.5	Mushrooms	0.4
Beef	0.8	Mutton	0.2
Cabbage	1.2	Orange	0.8
Carrots	1.2	Peas (dried)	3.0
Cauliflower	0.2	Pork	0.9-2.7
Cheese	0.7	Potatoes	2.2-3.2
Chicken breast	1.3	Salmon	4.5
Egg	0.2	Tomatoes	0.6
Grapefruit	0.1	Turnip	1.1
Halibut	1.1	Wheat	4.2
Lamb	0.8	Yeast (dried)	3-4

TABLE I.—Vitamin B_6 content of foodstuffs (mg. per kg.).

DAILY REQUIREMENTS IN HEALTH AND DISEASE

That vitamin B_6 is essential for health is amply demonstrated by the symptoms and signs which follow administration of the specific antagonist, desoxypyridoxine. In addition, some of the manifestations of multiple vitamin deficiencies in malnutrition states closely resemble the lesions produced by pyridoxine deprivation. Estimates of the adult daily requirement are of the order of 1 to 2 mg., and urinary excretion of pyridoxic acid, the end-product of vitamin B_6 metabolism, in health is usually in the range of 1.5 to 2 mg. a day.

Analysis of hospital diets has shown that these generally provide between 1 and 1.5 mg. of pyridoxine daily. Approximately 0.8 mg. is also produced daily by the microbial flora of the gut but the evidence is that this is excreted in the fæces and is not available for metabolic needs. Administration of antibiotics substantially reduces the amount produced in this way. It is difficult to assess the state of vitamin B_6 nutrition by determining blood levels since it is present in such low amounts. A better indication can be obtained by measuring the content of the white blood cells or by determining the level of xanthurenic acid excreted in the urine.

Studies in infants have shown that the average daily requirement is from 0.2 to 0.3 mg. a day, and this amount is generally available both to breast-fed infants and to those receiving the usual dried milk preparations. When the intake falls below 50 to 80 micrograms a day for a period of a few weeks symptoms and signs of deficiency rapidly arise.

Diets rich in protein and low in essential fatty acids slightly increase the requirement of vitamin B_6. So does hyperthyroidism. Also, some infants have an unusually high dietary requirement and are liable to show signs of severe deficiency in the few weeks immediately following birth. The reason for this is unknown.

DOSAGE, ABSORPTION AND STORAGE

Pyridoxine, pyridoxal and pyridoxamine are all rapidly absorbed from the gastro-intestinal tract and appear to follow the same metabolic pathway. When 100 mg. of pyridoxine hydrochloride are given orally about one-half can be accounted for in the urine within twelve hours. Most of this is in the form of pyridoxic acid. The other half is probably excreted in the form of unidentified metabolites. Sufficient vitamin B_6 for at least two months' needs appears to be stored in the body.

Since B_6 deficiency generally forms part of a more widespread vitamin deficiency disease it is rarely necessary to administer this vitamin alone. Diseases such as pellagra and beri-beri, already under treatment with their own specific vitamins, often show considerable subjective improvement following 50 mg. of vitamin B_6 orally or parenterally and in these diseases doses of this order by mouth should be continued until recovery is complete. Afterwards an adequate diet should provide all the necessary requirements.

Infants showing signs of deficiency should receive 5 to 10 mg. of pyridoxine in their feeds daily until recovery takes place. Injection is necessary only in the event of convulsions. If the deficiency is found to be due to the feeding of proprietary preparations devoid of vitamin B_6 then change to a more suitable preparation should be made. Only in those with an unusually high dietary requirement is it necessary further to supplement the vitamin intake.

THERAPEUTIC INDICATIONS OTHER THAN NUTRITIONAL

In addition to its use in nutritional deficiency states pyridoxine has been used clinically in a wide variety of conditions, but on the whole the results suggest that the vitamin has little or no therapeutic value.

Anæmias and blood dyscrasias.—When anæmia is a manifestation of a generalized deficiency state vitamin B_6 may produce a reticulocytosis. There is no valid evidence, however, that it is effective in the treatment of megaloblastic anæmias of the Addisonian type or of agranulocytosis.

Neuromuscular and nervous diseases.—In doses of the order of 50 mg. daily pyridoxine rapidly relieves the peripheral neuritis associated with the administration of large doses of isoniazid in the treatment of tuberculosis. It is also of value in preventing convulsions and epileptic fits in infants when these may clearly be attributed to vitamin B_6 deficiency. Attempts to demonstrate a deficiency in other epileptic states have not been successful.

Skin conditions.—Although infantile seborrhœa and adult seborrhœic dermatitis closely resemble the skin lesions produced by pyridoxine deficiency, these conditions show no marked response to vitamin B_6 therapy.

Nausea and vomiting.—Pregnant women given a test dose of tryptophane excrete abnormally large amounts of xanthurenic acid. The observation that this increased excretion may be restored to normal by giving relatively small doses of vitamin B_6 has led to the belief that certain manifestations of pregnancy such as nausea and vomiting are due to a specific deficiency.

Thus, it has occasionally been recommended for the prevention and treatment of this condition. The effects of intravenous injection of 100 mg. of pyridoxine in acute alcoholism reported by Martensen-Larsen (1954), however, are more characteristic of the placebo response than of the action of a vitamin. The evidence that vitamin B_6 in doses of the order of 100 mg. reduces nausea and vomiting associated with irradiation therapy is, perhaps, a little more convincing.

Atherosclerosis.—Although degenerative changes in the arterial walls of experimental animals may be produced by pyridoxine-deficient diets, it has not been shown so far that the administration of this vitamin prevents the onset of atherosclerosis in man. Nor is there much support forthcoming for the use of pyridoxine in the prevention of human dental caries.

TOXIC AND SIDE-EFFECTS

Vitamin B_6 is relatively non-toxic even in large amounts. Convulsions occur in experimental animals after the administration of doses of 1 g./kg. of body weight, but toxic effects have never been reported in man. Intravenous injection of doses as small as 20 mg. may produce small changes, an increase or a decrease, in blood sugar levels but these are not important clinically.

SUMMARY

Vitamin B_6 comprises three naturally occurring substances: pyridoxine, pyridoxal and pyridoxamine. Pure deficiency of the vitamin is rare in clinical practice for diets deficient in vitamin B_6 are also deficient in other members of the B group. A well-defined deficiency disease may, however, be produced by administration of the specific antimetabolite, desoxypyridoxine. The symptoms and signs of deficiency in adults include seborrhœa-like lesions of the skin, cheilosis, glossitis, weakness, dizziness and vomiting, and these may rapidly be relieved with pyridoxine by mouth in doses of 25 to 50 mg. daily. Vitamin B_6 deficiency may occur in infants receiving foods in which the vitamin has been destroyed by autoclaving; this manifests itself as irritation and convulsions and rapidly responds to the administration of pyridoxine.

The adult daily requirement of vitamin B_6 is 1 to 2 mg. and the infant requirement is 0.2 to 0.3 mg. It is widely distributed in foods, and diets adequate in caloric value are also generally adequate in vitamin B_6. Although it has been recommended clinically in a wide variety of conditions, the results of treatment are, on the whole, disappointing.

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PANTOTHENIC ACID AND BIOTIN

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WIDESPREAD interest was aroused by the discovery that pantothenic acid, a component of the vitamin B complex, was able to prevent the greying of the fur of rats maintained on a deficient diet. Hopes were engendered that this substance would be effective in man, restoring to normal hair becoming thin and grey. Although this therapeutic hope proved groundless, continued research has shown that this vitamin is of great importance.

The experimental work which led to the discovery of pantothenic acid may be briefly summarized as follows. A pellagra-like dermatitis developing in chicks on a restricted diet was noted in 1931, and subsequently it was shown that this could be prevented by a 'filtrate factor' from liver. This factor was able also to prevent the nutritional achromotrichia (greying of fur) developing in rats fed on a vitamin-B-deficient diet. It had long been realized that some unknown substance was required for the growth of yeast, and eventually it was shown by Williams, in 1933, that this was of such ubiquitous distribution that he called it pantothenic acid (*pantothen* = everywhere). Eventually this was isolated, its precise composition determined to be 1-hydroxy-2:2-dimethyl butyl-β-alanine, and in 1940 it was synthesized. It proved to be the substance in liver filtrate factor effective against chick dermatitis and the greying of hair in rats.

SOURCES

As its name implies, pantothenic acid is very widely distributed in foodstuffs, both animal and vegetable. Yeast, liver and egg-yolk are particularly rich in this vitamin, but no food is entirely devoid of it. Some bacteria can synthesize pantothenic acid, and it is produced in the gut of the ruminant animal although possibly not in the human alimentary canal. It is a water-soluble vitamin, unstable when subjected to heat, but forms a stable calcium salt.

MODE OF ACTION

That pantothenic acid is of great importance might be inferred from its wide distribution in living matter, and it was not long before biochemical research showed that the essential character of this vitamin is concerned with the part it plays in enzyme action. Enzymes, responsible for so many chemical changes in the body, are proteins. The substrate, or substance on which they act, is adsorbed on to the enzyme close to an active, or prosthetic, group. This group, which may be non-protein in nature, may be dissociable from the enzyme and is known as a coenzyme. Pantothenic acid is a component of coenzyme A which is of the utmost importance in many metabolic

processes. It is concerned in the processes of acetylation, such as occur in the detoxication of sulphonamides, and in the synthesis of acetylcholine. In particular, it catalyses the conversion of oxalacetic acid to citric acid, the first step in the tricarboxylic acid cycle of Krebs, the terminal oxidation pathway for both carbohydrates and fatty acids. Accordingly it is not surprising that a dietary deficient in this essential component should result in serious disturbance of health.

SYMPTOMS AND SIGNS OF DEFICIENCY

Reference has already been made to the nutritional achromotrichia which results in rats fed on such a diet but other abnormalities have been observed such as failure to grow, hæmorrhage and necrosis of the suprarenals, gastric ulceration, anæmia and leucopenia. Alloxan-diabetic rats have been found to be much more susceptible to pantothenic-acid deficiency than non-diabetic animals and it has been suggested that this may be accounted for by the fact that pantothenic acid appears to be of importance in the maintenance of the adrenal cortex. In dogs deficiency has led to gastroenteritis, impaired absorption of carbohydrate and protein, and anæmia, whilst disorder of the alimentary tract and anæmia have been produced in pigs and monkeys. Deficiency has been reported to cause depression of antibody formation. The action of 6-mercaptopurine in blocking nuclear mitosis is countered by coenzyme A. In addition to the dermatitis which is seen in chicks with pantothenic-acid deficiency, degenerative changes in the spinal cord have been observed, and changes referable to the nervous system have been reported in other animals. In dogs convulsions and coma have occurred, pigs have developed incoordination of gait, and ataxia has been noted in the monkey. The toxicity of streptomycin as evidenced by the impairment of balancing power when the drug is given to cats is reduced by the simultaneous administration of sodium pantothenate.

It is apparent therefore that gross deficiency of pantothenic acid in the diet can produce serious abnormalities. It must be remembered, however, that there is danger in assuming that conclusions drawn from animal experiments are applicable to the human subject. In fact no deficiency symptoms have been reported as occurring in man. An attempt was made to study the effect of deprivation of this vitamin in four human volunteers. They were given a diet deficient in pantothenic acid, but to aggravate the deficiency they were also given ω-methyl-pantothenic acid, an antagonist to the vitamin. The latter is one of a number of analogues of pantothenic acid which probably antagonize the action of the vitamin by blocking its entry into the important enzyme actions already mentioned and this particular antagonist had been shown to cause evidence of pantothenic-acid deficiency when administered to mice (although some recent workers have failed to confirm this). The volunteers developed clinical and biochemical abnormalities suggestive of adrenal cortical insufficiency and peripheral neuropathy. This abnormal state, however, was not immediately relieved by the

administration of pantothenic acid (4 g. daily) alone but rapid and complete recovery resulted when they were given a good mixed diet with multiple vitamins. It is not possible to be certain that the changes observed were due to deficiency of pantothenic acid alone, as these may have been attributable either to some toxic property of the antagonist or to the induction of a multiple vitamin deficiency.

THERAPEUTIC INDICATIONS

It can be concluded that the spontaneous development of a pantothenic-acid deficiency syndrome is highly improbable in view of the very wide distribution of the vitamin in foods. Nevertheless, pantothenic acid has been tried as a therapeutic agent in many disorders. In view of the absence of any evidence that greying of hair in the human adult was attributable to deficiency of the vitamin it is not surprising that its use proved of no value in restoring the normal colour. Achromotrichia has been reported in malnourished children in Nigeria, and it was believed that this was attributable to pantothenic-acid deficiency, since improvement was noted after administration of the vitamin. It is impossible to conclude that this element alone was the beneficial factor since these children were at the same time given a good mixed diet. The value of pantothenic acid in dermatology is doubtful, but it has been claimed that when massive doses (small doses were inadequate) are administered in combination with vitamin E it is effective in the treatment of chronic discoid, and subacute disseminated, lupus erythematosus, and may be of value as maintenance therapy in acute disseminated lupus erythematosus after initial control with steroids.

Several workers have used pantothenic acid in the treatment of post-operative paralytic ileus and benefit has been reported following intramuscular injections of 50 mg. A relationship between intestinal motility and serum potassium level exists and when the latter is low in the postoperative phase treatment with 500 mg. intramuscularly is stated to produce a rapid rise in the potassium level with restoration of intestinal motility. Pantothenic acid has been tried in the treatment of diabetic neuropathy, but without apparent benefit. High blood levels of pantothenic acid have in fact been stated to exist in this disorder. Failure of corticotrophin to produce eosinopenia, suggesting adrenal insufficiency, has been promptly corrected by a single oral dose of calcium pantothenate (1 g.) and it has been suggested that this might be tried in Addison's disease.

Experimental evidence of neurological abnormalities appearing with pantothenic-acid deficiency has led to its use in a variety of such disorders in man. One of the very trying complaints which was common among soldiers who became prisoners-of-war in Malaya was the 'burning feet' syndrome. This was certainly associated with malnutrition but the precise causation of the disorder is uncertain. It is not associated with true peripheral neuritis as local neurological signs are not found even when the trouble has persisted for months. It has been suggested that it may result

from degenerative changes in terminal sympathetic fibres to blood vessels, or to the liberation of some vasodilating substance. Claims have been made that a daily injection of 20 to 40 mg. of pantothenic acid produces rapid improvement. Recovery, however, takes place quickly on resumption of a well-balanced diet without this specific treatment. Recently, controlled observations were made on 60 patients whose principal complaint was burning and aching of the extremities and it was concluded that pantothenic-acid deficiency was not the cause of the disorder. Pantothenic acid has also been used in psychiatric practice. One report states that 18 psychotic patients who showed little or no response to convulsive therapy obtained full remission when intravenous injections of 100 mg. each of pantothenic acid and of nicotinamide were given daily for three weeks. Another worker found that when given intramuscularly in doses of 1.25 to 2.5 g. to patients receiving insulin shock therapy the duration of shock and the incidence of cerebral convulsions were reduced, whilst its daily administration led to deepening of the insulin shock so that the dose of insulin could be reduced. It was postulated that this therapy prevented blocking of the enzyme systems.

Recently pantothenic acid has been used in the treatment of neurotoxic symptoms developing with streptomycin therapy in tuberculosis. A series of 31 patients, all of whom showed definite evidence of vestibular damage, were treated with 50 mg. of pantothenic acid thrice daily, in the majority of cases streptomycin being continued or recommenced after an interval. This treatment is reported to have effected cures in 26 patients, four being improved, whilst in only one was it unsuccessful.

REQUIREMENTS

Pantothenic acid is essential. In the human body the evidence suggests that it cannot be synthesized and therefore it must be obtained from the diet. Since its distribution in foods is so wide and no deficiency syndrome has been discovered it can be assumed that it is supplied in adequate amount in any normal dietary. What is the precise daily requirement of the vitamin, however, is difficult to state. It is excreted in urine, sweat and milk. Various estimates of the average daily excretion have been made and this is probably 2.5 to 3.5 mg. Accordingly, one might speculate that the daily requirement of this vitamin is about 10 mg. As has already been mentioned much larger quantities have been used therapeutically but there seems little danger of toxicity. As much as 50 to 200 mg. per kg. per day, administered over a period of six months to monkeys, dogs and rats, did not produce any toxic manifestations or pathological changes.

BIOTIN

Biotin is another component of the B-complex. Its chemical structure is D-2′keto-3:4-imidazolido-2-tetrahydrothiophene-n-valeric acid, and it was synthesized in 1943. It seems certain that it plays a part in metabolic conversions, entering into several important enzyme reactions such as the fixa-

tion of carbon dioxide into aspartic acid, adenine, and citric acid, but its precise mode of action is not yet known. Like pantothenic acid it is of very wide distribution in foodstuffs, so that deficiency is unlikely to occur. There is, however, one well-known case in which the symptoms appeared attributable to biotin deficiency. This was an elderly Italian labourer who had suffered from extensive exfoliative dermatitis and conjunctivitis for years. His diet was remarkable: he consumed about six dozen raw eggs a week, and 1 to 4 quarts of wine a day! After two weeks' treatment in hospital on a liberal diet and injections of biotin the dermatitis largely disappeared.

It was known in 1927 that a diet containing a high proportion of raw egg-white was toxic to rats, but that this effect could be prevented by giving yeast or liver, the protective substance therein being called vitamin H. This was eventually identified with a crystalline substance in egg-yolk which had already been named biotin. The toxicity of egg-white was found to be due to one of its proteins, avidin, which combines with biotin rendering the latter unavailable to the body. Avidin is broken down by heat—hence cooked egg-white is innocuous. The requirements of biotin are extremely small, one ten-thousandth part of one milligram being sufficient to cure a rat of the effects of deficiency. Formerly this animal was used for the biological assay of biotin, deficiency of which causes changes in the skin and fur, particularly round the eyes producing the appearance known as 'spectacle-eye', stunted growth, and spasticity of gait. Biotin is essential for reproduction and lactation. Microbiological methods, studying the effect on the growth of yeast and certain bacilli, are now used as the means of assay of this vitamin.

REQUIREMENTS OF BIOTIN

No precise estimate can be given of the quantity of this essential substance which the human body requires. It has been estimated that with a normal diet between 11 and 183 micrograms are excreted daily in the urine, but this quantity is only slightly reduced when the diet is deficient. Biotin is synthesized by bacterial action in the bowel and this is doubtless an important source. This synthesis can be inhibited by large doses of sulphaguanidine or sulphasuxidine, but not with ordinary dosage or other sulphonamides. Human requirements may be deduced to some extent from a study carried out on volunteers fed on a biotin-deficient diet in which 30 per cent. of the available calories were obtained from egg-white. Over a period of four to ten weeks a definite clinical syndrome developed, characterized by brawny desquamation of the skin, atrophy of the papillæ of the tongue, lassitude, and mild anæmia. Daily injections of 150 to 300 mg. led to prompt recovery within four to five days. Whilst it may be assumed that 150 mg. a day should be at least adequate, larger doses do not appear to cause toxic effects. Mice have been given intravenous injections of biotin in doses of 1 g. per kg. without evidence of ill-effect, but also without beneficial effect on regeneration or healing of tissue.

THERAPEUTIC USE OF BIOTIN

Although deficiency of biotin seems an unlikely event, the results obtained from experimental work have led to trial of biotin as a therapeutic agent in a variety of conditions. The most satisfactory results have come from workers who have used it in the treatment of exfoliative dermatitis in infants, several reporting good results from daily injections of 5 mg. for one to two weeks. It has also been used in seborrhœic dermatitis in children; some cases being recorded as showing a good response. Following the demonstration that embryo and tumour tissues contained a high concentration of biotin, attempts have been made to arrest the growth of neoplasms by trying to effect biotin deficiency, either with a deficient diet or by giving enormous quantities of egg-white, but no beneficial effects have been obtained.

SUMMARY

Pantothenic acid and biotin, two of the constituents of the B complex, have been isolated and their precise chemical composition is known. Both vitamins are widely distributed in foodstuffs and evidences of deficiency are unlikely to arise in man. Animals fed on diets deficient in either develop various abnormal signs. Largely from the analogy of these to disease processes in man both pantothenic acid and biotin have been used therapeutically. Beneficial results have been claimed, but confirmation is desirable. Both play an essential part in enzyme action. Pantothenic acid is a component of coenzyme A which is of great importance in the ultimate breakdown of carbohydrates and fats in the body. Further study of these vitamins must increase our knowledge of biochemical processes and should lead ultimately to a better understanding of certain pathological states.

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VITAMIN B_{12} (CYANOCOBALAMIN)

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VITAMIN B_{12}, or cyanocobalamin (5:6-dimethyl-α-benziminazole-cyanocobamide), is a cobalt-containing hygroscopic red crystalline compound that is odourless, tasteless and is soluble in water, less soluble in alcohol and insoluble in most organic solvents. It is stable in neutral aqueous solutions, which can be sterilized by autoclaving. It was isolated from animal liver in 1948 by Folkers and his colleagues, and by Smith and his colleagues, and was shown to be identical with the liver factor noted by others to be necessary for the growth of certain micro-organisms and animals.

CHEMISTRY AND PHARMACOLOGY

The molecule of cyanocobalamin (fig. 1) contains a central cobalt atom linked to a –CN group, and its structural formula was finally elucidated in 1955 with the aid of x-ray crystallography by Hodgkin and her colleagues and by Bonnet and his colleagues. The replacement of the –CN group by other radicals produces similar active and closely related cobalamins.

Cyanocobalamin is stored in the liver and also other organs and is probably loosely bound to α-protein until required for use in the body. There is evidence to suggest that it is fundamentally concerned in the synthesis of labile methyl groups, probably from more highly oxidized precursors, for the synthesis of certain essential substances but is not concerned directly with transmethylation which may be brought about under the influence of folic acid. It is probably associated, in some way that is not clear, with folic acid in the metabolism of purines and pyrimidines leading to the synthesis of nucleoproteins and thence to the production of normal normoblastic hæmopoiesis in the bone marrow: a marked deficiency of cyanocobalamin leads to a megaloblastic hyperplasia of the marrow and the production of pernicious anæmia with or without postero-lateral sclerosis of the cord.

Cyanocobalamin appears to be necessary for the normal growth of chicks and certain other animals as well as many micro-organisms and has been included in the so-called animal protein factors. Its influence on the normal growth of children has not yet been proven.

Estimation of cyanocobalamin.—The estimation of cyanocobalamin in serum depends on a biological method of assay based on the stimulation of growth of certain micro-organisms such as *Euglena gracilis* and *Lactobacillus leichmanii*. In normal persons the serum cyanocobalamin value varies over the wide range of 140 to 900 millimicrograms per millilitre. On the other hand, in relapsed pernicious anæmia the serum cyanocobalamin is usually

less than 80 millimicrograms per ml., whilst in subacute combined degeneration of the cord there may be considerably this. The determination of the degree of intrinsic factor activity is ca out by the use of cyanocobalamin labelled with radioactive cobalt—using either Co^{60}, Co^{58} or Co^{56}, the two latter being better since they have half-lives of only 72 days.

A test dose (1 or 2 mcg.) of the labelled cyanocobalamin will not be absorbed if given orally to a patient with pernicious anæmia or faulty absorption of cyano-

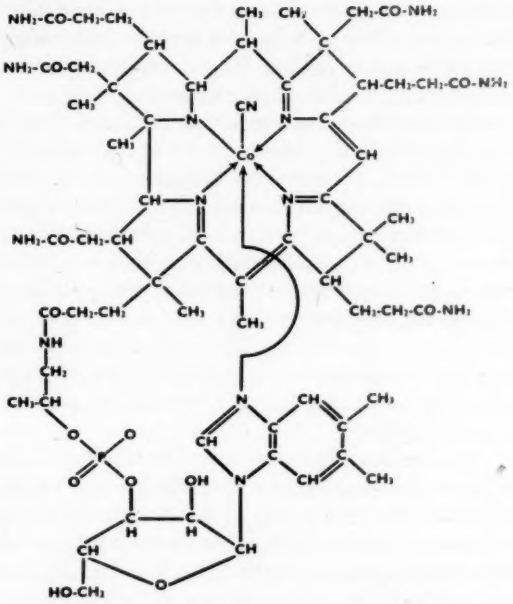

Fig. 1—Structure of cyanocobalamin.

cobalamin and so can be measured in the fæces. If intrinsic factor is also given at the same time and then a 'flushing' dose of 1 mg. of non-radioactive cyanocobalamin given parenterally, the labelled cyanocobalamin now absorbed will be excreted in the urine and can be measured.

SOURCE AND REQUIREMENTS

Cyanocobalamin occurs naturally in such food sources as liver, kidney, heart muscle (and, to a lesser extent, in other meat), fish, egg yolks and cheese, but not in vegetables. Large quantities of cyanocobalamin and its analogues can also be obtained from fermented rumen or gut contents of cattle, and fæces from pig n, as well as from sewage sludge; in all of these it has been pr by biosynthesis under the influence of many micro-organisms, so of which, e.g. *Streptomyces griseus*, are now used commercially to pro uce large quantities of cyanocobalamin and its analogues by controlled fermentations.

Whilst cyanocobalamin may be associated with several different metabolic processes in the body, its main function would appear to be due to its identity with Castle's 'extrinsic factor' in the food.

The normal daily requirement appears to be about 1 mcg. The absorption of cyanocobalamin from the alimentary tract, however, is not a simple procedure although it has been shown that an occasional patient with pernicious anæmia can absorb 5 to 100 mcg. or more daily when given orally without the addition or help of intrinsic factor, producing and maintaining satisfactory remission. This is very exceptional; ordinarily, an adequate supply of intrinsic factor is needed for the proper normal absorption of cyanocobalamin through the intestinal mucous membrane.

The exact nature of the intrinsic factor is not known but it appears to be a muco-protein secreted in the human stomach from special cells situated in the cardia and fundus. Its exact mode of action is not yet clear but the available evidence would suggest that its function is to make available for absorption the cyanocobalamin present in the food, either by liberating it from a bound form, and/or possibly combining with it to form a more easily absorbed complex; other suggested mechanisms and speculations have much less, if any, convincing supporting evidence.

CAUSES OF CYANOCOBALAMIN DEFICIENCY

Cyanocobalamin deficiency may follow any break in, or interference with, normal gastro-hæmopoiesis.

Nutritional deficiencies.—An inadequate intake of cyanocobalamin-containing foods, as in starvation or severe dietetic restrictions that may be associated with abnormal food fads such as extreme vegetarianism and following excessive prolonged dieting after gastro-intestinal ulceration, may lead to an initial deficiency of cyanocobalamin (extrinsic factor). In these patients there may be severe malnutrition with evidence of deficiencies of other vitamins, but there will usually be a delay in the manifestations until the body's stores of cyanocobalamin have been depleted and the serum cyanocobalamin has fallen to a very low level (less than 100 millimicrograms per ml.). These cases usually do not have achylia gastrica and respond very well and quickly to even small doses of cyanocobalamin and a normal diet.

Deficiency of intrinsic factor (*hæmopoietin*).—The majority of conditions associated with cyanocobalamin deficiency arise from faults in the alimentary tract. The most important is the absence of intrinsic factor from the stomach, which may be noted most commonly of all in pernicious anæmia, in which the cells secreting intrinsic factor in the gastric mucous membrane have atrophied (an inherited familial fault) so that there is faulty absorption of cyanocobalamin. This also follows the destruction of the gastric mucosa by disease—alcoholic or chronic gastritis, toxins, or corrosive poisons—and usually some three to ten years after total gastrectomy (but very rarely after gastroenterostomy) when the body stores of cyanocobalamin have

become exhausted, the serum cyanocobalamin usually being less than 80 millimicrograms per ml.

Defective absorption of cyanocobalamin or its destruction in the intestinal canal, although gastric secretion of intrinsic factor and hydrochloric acid may be normal.—This may arise from various causes—severe dietetic malnutrition, occasionally when intestinal parasites such as *Diphyllobothrium latum* are present, chronic intestinal stenosis due to tuberculosis or cancer, multiple fistulæ, dysfunction of the small intestine associated with obstruction, or blind loops, again associated as a rule with a considerably reduced serum cyanocobalamin. Occasionally sprue, idiopathic steatorrhœa and megaloblastic anæmia of pregnancy may be causes under this heading, with diminished serum cyanocobalamin values, but more usually these conditions are related to folic-acid deficiency rather than to cyanocobalamin deficiency.

Other causes.—On rare occasions when the available cyanocobalamin in the body is inadequate to meet increased requirements due to disease, abnormal demands (e.g. pregnancy), or disorganization of certain intermediate metabolic processes, for which cyanocobalamin may be necessary.

It must be remembered that certain megaloblastic or macrocytic anæmias may not be associated with either cyanocobalamin deficiency, the serum cyanocobalamin being normal, or with achylia gastrica. Such anæmias may occur in association with pregnancy or the puerperium, achrestic anæmia, sprue, idiopathic steatorrhœa and liver disease.

SYMPTOMS AND SIGNS

The outstanding and most important symptoms and signs of a cyanocobalamin deficiency, with low serum cyanocobalamin, are those associated with pernicious anæmia, subacute combined degeneration of the cord, and some megaloblastic anæmias. Thus, the patient may complain of sore mouth and tongue, often with recurring ulceration, the tongue showing typical atrophic glossitis; flatulent dyspepsia especially after meals is a common symptom, often of long duration. In due course dyspnœa, palpitation and tiredness on slight exertion, accompanied by increasing pallor and anæmia, become marked. Examination shows typical megaloblastic hyperchromic anæmia with anisocytosis and poikilocytosis, some normoblasts in the peripheral blood and a characteristic megaloblastic hyperplastic bone marrow (showing megaloblasts in large numbers, giant leucocytes and giant megakaryocytes), which shows a rapid return to a normal normoblastic type within one to three days of treatment with cyanocobalamin. There may be abnormal enlargement of cells of other tissues, as in the mucous membranes of the mouth, stomach and vagina.

Definite neurological changes may occur even in the absence of any anæmia or obvious marrow changes, and subacute combined degeneration of the spinal cord seems to be due to a pure deficiency of cyanocobalamin (with a negligible serum cyanocobalamin level), which can definitely be produced or made worse by folic acid; folic acid is therefore contraindicated

in the treatment of this disease. The neurological symptoms and signs usually begin as a peripheral neuritis with pins and needles and numbness in the hands and feet, going on later to more serious involvement of the spinal cord with all the features of well-developed subacute combined degeneration of the spinal cord, with loss of joint sense and vibration sense, incoordination, extensor plantar responses, spastic paraplegia and loss of bladder and rectal control. In some cases cerebral disturbances may be noted, usually mild in character such as loss of memory, restlessness, irritability, but these may become more severe with slowed cerebration, depression, confusion, delirium, hallucinations, psychoses and occasionally severe dementia, which is usually irreversible. Sight may be impaired and associated with retinal hæmorrhages, central scotoma and optic atrophy, which may occasionally be early signs. Whilst gross deficiencies of cyanocobalamin lead to these obvious signs and symptoms, there are no outstanding or certain clinical indications when there are much lower degrees of cyanocobalamin deficiency.

Cyanocobalamin deficiency has been thought to be a factor in the development of peripheral neuritis in chronic alcoholics, in diabetes mellitus especially when retinopathy is present, and in tabes dorsalis, and is also said to have some association with trigeminal neuralgia and herpes zoster.

INDICATIONS AND DOSAGE IN PERNICIOUS ANÆMIA

The indications for giving cyanocobalamin therapeutically are simple: it should be given to any patient who shows a cyanocobalamin deficiency. This can be determined by estimating the serum cyanocobalamin or the cyanocobalamin absorption, but in the great majority of cases the indications are a megalocytic, hyperchromic anæmia with a megaloblastic bone marrow, usually associated with an achlorhydria gastrica. It should be borne in mind that macrocytic or megaloblastic anæmia due to folic-acid deficiency will not respond to cyanocobalamin therapy—such patients are usually those with sprue, idiopathic steatorrhœa and megaloblastic anæmia of pregnancy.

The dosage varies according to the severity of the anæmia and the presence of neurological changes, the type of preparation of cyanocobalamin used and its mode of administration.

Parenteral.—As it is important to obtain a good rapid remission, the quickest, most economical and certainly the most effective way is to give cyanocobalamin subcutaneously or intramuscularly in doses of about 250 mcg. twice or three times weekly for the first two or three weeks until the blood count shows a rapid response to treatment (the earliest indication is usually a rapid increase in reticulocytes during the first ten days with subsequent progressive increase of red cells and hæmoglobin to normal); the marrow changes very rapidly to normal normoblastic activity after the first few days of active treatment. The dose can then be reduced to 250 mcg. once weekly until the blood count is quite normal, which should be in four to six weeks. Thereafter the maintenance dose will probably be about 100 to

250 mcg. weekly, fortnightly or three-weekly, according to the particular patient's needs. This dose must be regulated by the blood count and the clinical condition of the patient and may need some variation at different times of the year; it should always be increased when infections or other conditions supervene.

For patients with subacute combined degeneration of the cord a full dosage of 250 mcg. of cyanocobalamin on three or more days every week must be given and *continued indefinitely* until the symptoms and signs are relieved, for the blood count alone in these cases is not a sufficient guide.

Snuff.—An alternative, and occasionally effective, route for the treatment of some patients with pernicious anæmia is to insufflate cyanocobalamin into the nose using a special insufflator into which can be placed a capsule containing 100 mcg. of cyanocobalamin. The initial daily dose is 2 to 3 capsules of 100 mcg. each, reducing to 1 to 2 capsules as the blood count improves to normal; the maintenance dose is 100 mcg. once or twice weekly.

Oral preparations of cyanocobalamin, alone or combined with intrinsic factor, sorbitol, 'peptides' and mixtures of intrinsic factors with peptides, have been recommended. None of these preparations is completely reliable and their clinical effects cannot be compared with the absolute certainty of the parenteral administration of cyanocobalamin. Claims have been made that these oral preparations of cyanocobalamin (in varying dosages of 10 to 100 mcg.) will produce and maintain normal remissions, but the long-term effects are not so certain and there is no doubt that some of the patients so treated require increased doses later and many show falling blood counts and fail to maintain their improvement. Time alone will show the place, if any, for these preparations in the therapy of pernicious anæmia.

TREATMENT OF OTHER CONDITIONS

Cyanocobalamin has been recommended for the treatment of many other conditions but usually in much greater dosage. Thus, for the relief of trigeminal neuralgia and herpes zoster a dosage of 1000 mcg. daily for ten to fifteen days, thereafter twice weekly, has been recommended and marked improvement has been claimed. Further maintenance therapy may be needed subsequently for varying periods of time.

Migraine and asthma have been said to show improvement with similar large doses of cyanocobalamin, but this has not received much confirmation in any reasonable series of cases. Polyneuritis associated with severe diabetes mellitus and with chronic alcoholism is said to show some improvement after intensive cyanocobalamin therapy (1000 mcg.), but relapses usually occur and there may not be much real improvement in the long run.

TOXICITY

Apart from a few patients recorded as showing allergic reactions after cyanocobalamin, no toxic or serious ill-effects have been reported after the therapeutic use of cyanocobalamin, even in large doses for long periods.

VITAMIN E

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THE story of vitamin E has been one of the most chaotic in modern medicine. In the past thirty-five years, since Evans and Bishop first postulated its existence, and more particularly in the past twenty years since its isolation and synthesis, a vast literature has accumulated supporting the therapeutic value of the tocopherols in many of the diseases afflicting man. Critical analyses of these claims, however, the failure of more recent investigations to substantiate previous reports, and the inability to correlate the findings in experimental animals with human disease have all served to temper the original enthusiasm. Indeed, the pendulum has begun to swing and, encouragingly, recent articles appearing on vitamin E have been, for the most part, critical and analytical, only rarely hailing the tocopherols as a therapeutic panacea. In this article we propose to review briefly what is known concerning their proper place in medicine today.

The first and most disconcerting fact to be appreciated is that no deficiency syndrome in man has been reported to date, and therefore a discussion of the practical therapeutic aspects concerning the tocopherols is necessarily limited. It was not until after 1944, when analytical procedures became available for determining the vitamin E content of food as well as its levels in human blood and tissues, that reliable information relating this substance to human disease was obtained. With the advent of these procedures it immediately became apparent that vitamin E deficiency had been unjustly incriminated as an etiological factor in many diseases.

SOME MISCONCEPTIONS

Vitamin E was originally characterized as the 'anti-sterility' vitamin on the basis of the observation that female rats, fed a diet deficient in this substance, were able to conceive but had resorptive abortions in early pregnancy. This observation led to the belief that habitual abortions in women were due to a human deficiency state with respect to vitamin E. Control studies substantiating this claim, however, were entirely lacking. In addition, supporters of this theory overlooked the statistical evidence that a woman who has two consecutive miscarriages has a one to three chance that she will not have another. Particularly important were the findings of Scrimshaw (1952) and others indicating no significant difference in tocopherol serum levels in 69 patients with pre-eclampsia, 16 with essential

hypertension and 25 with premature labour, in comparison with 197 normal pregnant women at corresponding stages of pregnancy. Included in this study was the observation that 42 women who aborted at nine to sixteen weeks had an average serum tocopherol level of 0.96 mg. per cent., compared with 36 normal pregnancies of similar duration who had serum levels of 1.02 mg. per cent., a difference of no statistical significance. Scrimshaw concluded from his study that there was no evidence that the difference observed was primarily or in any way related to the etiology, pathogenesis or therapy of abortions. Comparable findings were reported by Engle (1952), who stated that the vitamin E serum level was not reduced in patients with habitual abortions and that vitamin E supplements did not help the prognosis in these patients. In accordance with these findings are the lack of any consistent variation in vitamin E levels with the phase of the menstrual cycle and its ineffectiveness as an agent in the control of menopausal symptoms.

Another observation made in experimental animals, fed on a diet deficient in the tocopherols, led to the misconception that various muscle disorders of man were related to vitamin E deficiency. In these laboratory animals a syndrome of hind-leg myopathy developed which clinically mimicked muscular dystrophy with a histopathology not unlike the picture encountered in human disease. It is now known, however, that people with various muscle disorders, such as muscular dystrophy, muscular atrophy and amyotrophic lateral sclerosis have normal tocopherol serum levels and that no beneficial effect on the progress of the disease accrues from the use of vitamin E. It is of interest to note that in a study on the intestinal absorption of this vitamin, reported by Rosenkrantz *et al.* (1952), a patient with muscular dystrophy was selected to represent a normal control with reference to vitamin E metabolism.

The value of vitamin E in the treatment of various cardiovascular diseases can be rapidly summed up by referring to the comment of the Council of Pharmacy and Chemistry, in 1950, which stated unequivocally that vitamin E had no value in the treatment of coronary artery disease, hypertension or rheumatic heart disease. Although some reports have commented favourably on its beneficial effects in the treatment of intermittent claudication, no adequate control series exist to support this contention and the natural history of this disorder is too variable to draw conclusions without a carefully controlled study. Reports of its efficacy as a therapeutic agent in diabetes mellitus, nephritis, burns, frostbite, and thrombophlebitis likewise lack effective proof. Similarly with the evidence on hand, one may well reserve judgment as to the place of tocopherols in the therapy of Dupuytren's contracture and Peyronie's disease.

NORMAL VALUES

Development of reliable analytical methods has led to the collection of

much data concerning the normal and abnormal serum and tissue tocopherol in man, and greatly increased the information concerning the metabolism of vitamin E in man. Normal values of serum tocopherol in man average 1 mg. per cent. in adolescents and young adults, slightly higher in older adults, whilst in the newborn lower levels of 0.23 mg. to 0.4 mg. per cent. are encountered. Deviations from normal are found in various diseases.

VITAMIN E EXCESS

Before reviewing what information exists on human deficiency states of vitamin E a brief comment on tocopherol excess in man is warranted. Some diseases characterized by hyperlipæmia and hypercholesterolæmia, such as nephrosis, diabetes mellitus, some instances of atherosclerotic vascular disease and the xanthomatoses, are associated with elevated serum tocopherol levels. This observation is considered to reflect only the increased serum-carrying capacity of fat-soluble substances such as vitamin E. No specific symptoms have been related to the excessive vitamin E levels found in these disorders. Hillman, in 1957, reported a human experiment in which a healthy physician ingested a total of 286 grammes of alpha-tocopherol over a 93-day period, which raised his serum level from a control normal of 1.15 mg. per cent. to 2.26 mg. per cent. during the course of the experiment. A four-gramme daily dose did not alter the serum level to any significant degree, compared with a two-gramme daily dose. Although most authors agree that creatinuria is decreased when vitamin E is given, in this study significant and inexplicable increases in creatinuria were observed in the test period. Deltoid muscle biopsy, 17-ketosteroid determinations, liver-function tests and bleeding tendency all remained normal. No unequivocal evidence of clinical toxicity was observed. The subject of the experiment, however, did develop stomatitis, and towards the termination of the test period significant abdominal distress, diarrhœa, weakness and fatigability occurred, the significance of which was not clear.

VITAMIN E DEFICIENCY

Deviations towards deficient serum levels are found in a variety of diseases associated with malnutrition and particularly in those diseases associated with steatorrhœa, such as cœliac disease, sprue, fibrocystic disease of the pancreas and also in obstructive jaundice.

Pappenheimer and Victor, in 1946, reported four patients who succumbed after prolonged illnesses with diarrhœa and/or nutritional œdema in whose livers 'ceroid' pigment was present; they related this finding to a vitamin E deficiency. This, they felt, correlated with the finding of 'ceroid' pigmentation in vitamin-E-deficient rats and dietary cirrhosis in rats. Serum or tissue tocopherol levels, however, were not reported and the authors pointed out that this pigment was also found in hæmochromatosis where vitamin E deficiency was not a factor and that in human cirrhosis the tocopherol levels were often normal. Popper *et al.* (1949) also reported on tocopherol

levels in various disease states and generally noted diminished levels in cirrhosis although there was much overlapping between normals and cirrhotics. Klatskin (Klatskin and Krehl, 1950; Klatskin and Molander, 1952) has also studied vitamin E in cirrhosis and noted diminished levels in some cirrhotics, but with wide variations. He found normal values of 1.23 mg. per cent.$\pm$0.31 mg. per cent., compared with values in hospitalized controls of 1.02 mg. per cent.$\pm$0.37 and values in cirrhotics of 0.95 mg. per cent.$\pm$0.32. His studies indicated that the deficiency was apparently related to diminished tissue stores rather than to faulty absorption. He ascribed no symptoms in the cirrhotics to this defect.

In 1956, Woodruff reported the first well-documented case of vitamin E deficiency in a man with xanthomatous biliary cirrhosis. The finding of negligible amounts of serum tocopherol was attributed to the prolonged low-fat diet prescribed for the hyperlipæmia of this disease, with resultant failure to absorb the fat-soluble vitamin E. Pentosuria and creatinuria were present when vitamin E was absent from the serum. When serum levels were restored to normal, pentosuria and creatinuria returned to normal. The increased red-cell hæmolysis *in vitro* with hydrogen peroxide also returned to normal when vitamin E supplements were administered. Nitowsky *et al.* (1956) found similar effects on creatinuria and red-cell hæmolysis in a child with cystic fibrosis of the pancreas, but noted that there was no evidence of improved muscle power after tocopherol administration. The hæmolysis test has been further studied by Horvitt *et al.* (1956), who concluded that this test was a complicated assay and was dependent upon more than the vitamin E level of the serum; they noted that it took many months for the hæmolysis test to return to normal after repletion with vitamin E and that there was no close correlation between the serum level and the extent of the hæmolysis.

REQUIREMENTS AND SOURCES

From this evidence it can be deduced that little information exists about man's requirements of vitamin E. No clinical syndrome indicating deficiency or excess of this vitamin has been clearly defined and only in advanced states of malnutrition of various etiologies has it occasionally been shown to be deficient. Repletion of vitamin E in these latter patients has offered no clinical improvement nor altered the progress of the disease.

Another approach has therefore been utilized to arrive at man's approximate requirements. The total tocopherol content of average diets has been analytically determined and found to approximate 15.7 mg. a day in Holland and 25.7 mg. a day in the United States. These values represent total tocopherol content (alpha, beta, gamma), and since the alpha form is preferentially absorbed from the human gastro-intestinal tract and is the form in which it is found in man's serum and tissues, correction is made for this value on the basis that 50 to 60 per cent. of this total is in the alpha form.

It is therefore concluded that approximately 14 to 19 mg. (13 to 17 i.u.) of alpha-tocopherol a day is the average intake of this substance and represents the normal requirement. Harris *et al.* (1950) obtained similar results but, based on the 'physiological weight', they felt that 30 i.u. of vitamin E daily was a more correct value.

The tocopherol content of almost all foods has been determined (Quaife *et al.*, 1956; Harris *et al.*, 1950). Generally, vegetable oils are the best source of vitamin E and animal oils, although containing less, have considerable quantities. Wheat germ oil has 60 to 70 mg. of alpha-tocopherol per 100 g., cotton seed oil 56 mg. per 100 g., margarine 28 mg. per 100 g., peanut oil 11 mg. per 100 g. and soya bean oil 10 mg. per 100 g. The tocopherol content of fruits is almost exclusively in the alpha form and varies from about 0.23 to 0.72 mg. per 100 g. Among the vegetables, turnips and turnip greens have the highest contents of alpha-tocopherol, approximating 2.3 mg. per 100 g. The tocopherol content of carrots and celery is entirely in the alpha form but totals somewhat less than turnips. Many other vegetables, such as wax beans, have a high total tocopherol content, but the percentage in the alpha form is extremely low. Meat is a relatively poor source of vitamin E but two eggs contain 2.4 mg. of tocopherol, 60 per cent. of which is in the alpha form. Fish with a high fat content, such as haddock and sardines, are a rich source of vitamin E. Cow's milk is a poor source; butter contains 2.4 mg. per 100 g. Among the cereals, maize with 0.84 mg. per 100 g., and oatmeal with 1.94 mg. per 100 g., have the highest vitamin E content. It has been demonstrated that there is a great vitamin E loss in cereals during processing.

The loss of vitamin E during cooking is variable. Deep fat frying is very destructive with a 70 to 90 per cent. loss. In the baking process some, but considerably less, is destroyed. Other forms of cooking have little effect on the tocopherol content.

Specialized therapeutic diets contain, on an average, lesser amounts of tocopherol than the daily average diet. Thus, the low-sodium, 1,900-calorie, diet contains 7.22 mg.; the 1,600-calorie diabetic diet contains 8.6 mg.; and the 1000-calorie reducing diet 4.3 to 6.6 mg.

Despite its equivocal place as a therapeutic agent it is interesting to note that many different preparations of vitamin E are available commercially in widely varying dosages. Synthetic preparations of alpha-tocopherols are available in oral and parenteral forms and are sold both in combination with other vitamins and as vitamin E alone. Dosages of individual preparations available range widely. A recommended dosage is, of course, not established with any assurance because of the existing gaps in our knowledge concerning man's need for this substance. The absence of convincing data to support its usefulness in any known disease state, despite intensive investigations to define its function, indicates the insecure place of the tocopherols in therapeutics today.

FUTURE PROSPECTS

In concluding this brief review, however, it might be well to look momentarily towards a brighter side. It might be argued, teleologically, that its presence in nature and more particularly its consistent occurrence in man, suggests some role, as yet undiscovered, for this substance. Perhaps supporting this conjecture are recent analytical studies (Horvitt *et al.*, 1956; Rosenkrantz, 1956; Mei Yu Dju *et al.*, 1957) which have shown persistently that, in addition to its antioxidant activities in biological systems, vitamin E is present in highest concentration in the pituitary, adrenals, and testes. In addition, it has been shown conclusively that oxygen consumption of adrenal tissue and adrenal-reducing substances increases in vitamin E deficient rabbits. These isolated findings have at least served to focus attention in a new and refreshing direction. Out of these studies has grown speculation on the potential existence of an oxidation-reduction system relating tocopherylhydroquinone and tocopherylquinone to the steroids; these interesting studies may throw new light on the function of vitamin E. The possibility of a biochemical role to explain the relatively high concentration of vitamin E in endocrine glands has also arisen from these recently accrued data.

SUMMARY

In our present state of knowledge, it would seem wisest to conclude that the tocopherols, except for their possible use in severely malnourished states, should be left in the hands of the research investigator and biochemist until their therapeutic value is more clearly defined.

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VITAMIN K

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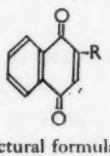
IN 1934, H. Dam, in Copenhagen, described a bleeding disorder in chickens reared on purified diets. Since the abnormality was corrected by the addition of greenstuff to the food it was ascribed to deficiency of ascorbic acid until it was shown that, unlike ascorbic acid, the curative substance was fat-soluble. The disorder was accompanied by a prolonged coagulation time and it was therefore postulated that the chicks lacked a new fat-soluble 'Koagulation Vitamin' or vitamin K. During the last few years this deficiency disease has caused heavy mortality among poultry housed on a commercial scale under highly artificial conditions. Vitamin K deficiency has been produced experimentally in a number of laboratory animals, although never in man, by feeding diets lacking in this vitamin. A deficiency syndrome, however, does occur in man as the result of factors other than dietary lack.

When it was shown that the abnormality of coagulation in affected chickens could be corrected by adding to the blood crude preparations of chick prothrombin, it was supposed that lack of vitamin K led to prothrombin deficiency. Subsequent careful study of the abnormality, especially in man, has revealed a deficiency of other factors also, for example factors V and VII, so that the disorder of coagulation characteristic of vitamin K deficiency, or produced by administration of an antivitamin K, is complex.

CHEMISTRY AND PHARMACOLOGY

In 1939, a highly active, pure substance called vitamin K_1 was isolated from alfalfa and it was synthesized shortly afterwards. About the same time vitamin K_2 was isolated from putrefying fish meal. Vitamin K activity is in fact possessed by several naturally occurring substances (phthiocol for example) and a large number of synthetic compounds, some of which are more potent than vitamin K_1 itself. These active substances are derivatives of naphthoquinone (fig. 1). One of the most biologically active of them is 2-methyl-1:4-naphthoquinone (menaphthone B.P.; menadione U.S.P.). This



Vitamin K_1; R= phytyl-
Vitamin K_2; R = di-farnesyl-
Menaphthone; R = CH_3

FIG. 1.—Structural formula of vitamin K_1, vitamin K_2 and menaphthone.

substance is not water-soluble, but stable water-soluble derivatives of it can be prepared so that vitamin K can be given by mouth or by intra-

muscular or intravenous injection. Table 1 gives details of some of the vitamin K preparations now available.

Although vitamin K exercises its main physiological effect on blood coagulation, it does not affect the process directly. Vitamin K deficiency is characterized by a reduced concentration of prothrombin in the plasma, that is by a prolonged prothrombin clotting time, but the vitamin does not

Menaphthone B.P. (2-methyl-1:4-naphthoquinone). Oil soluble. 'Prokayvit' (B.D.H.) 1 ml. = 5 mg. 5 mg. per day by intramuscular injection. 'Hykinone' (Abbott) is an isotonic aqueous solution of menaphthone and sodium bisulphite (1 ml. = 5 mg.) suitable for subcutaneous, intramuscular or intravenous injection. Dose 2.5 to 5 mg. twice a day. Water-soluble derivatives of menaphthone (menadione U.S.P.) are popular in the United States but are used relatively little in this country.
Acetomenaphthone B.P. (2-methyl-1:4 naphthohydroquinone diacetate). Oil soluble. 'Kapilon' (Glaxo); 'Prokayvit Oral' (B.D.H.); 'Vitavel K' (Vitamins Ltd.). Tablets usually of 10 mg. Orally in doses of 20 to 30 mg. per day. If oil-soluble preparations are given to patients with obstructive jaundice bile salts should be given at the same time to promote absorption.
'*Synkavit*' (Roche): the diphosphoric ester of 2-methyl-1:4 naphthohydroquinone bis-(dihydrogen phosphate). This is water soluble. Available as tablets (calcium salt) of 10 mg. or in ampoules (sodium salt) of 1 mg., 10 mg. or 50 mg. in 1 ml.
Phytomenadione (Vitamin K_1; 2-methyl-3-phytyl-1:4-naphthoquinone). Oil soluble. 'Konakion' (Roche). A water-miscible solution in gelatin capsules (10 mg.) for oral use, or in ampoules (1 ml. = 10 mg.) for intramuscular or intravenous injection. Dose 10 to 20 mg. 'Mephyton' (Merck Sharp & Dohme). As tablets of 5 mg. or in an emulsion prepared with lecithin (1 ml. = 50 mg. vitamin K_1) for intravenous injection.

TABLE I.—Some vitamin K preparations.

form part of the prothrombin molecule. It is necessary, possibly as a co-enzyme, for the synthesis of prothrombin by the liver. In addition to the well-established role of the vitamin, and its synthetic analogues, in maintaining normal coagulation, there is inconclusive evidence that vitamin K may activate oxidative phosphorylation.

SOURCES AND DAILY REQUIREMENTS

The main dietary source of vitamin K is the green parts of vegetables, particularly of the brassica family. The vitamin K content of the diet, however, is unimportant, as vitamin K deficiency in man is not a dietary lack but a conditioned deficiency and there are readily available potent preparations that can be given by mouth.

The daily requirements cannot be stated because little is known about the amounts that may be stored in the body. Furthermore, unknown but nutritionally important quantities are synthesized by the bacteria of the bowel and subsequently absorbed. As little as 1 mcg. a day is said to be sufficient to correct the coagulation defect in the blood of new-born infants suffering from a conditioned deficiency of vitamin K. There have been a few

reports of deficiency of vitamin K occurring in adults as the result of inadequate diets but this is very rare, even in persons suffering from gross vitamin deficiency syndromes such as pellagra and scurvy.

VITAMIN K DEFICIENCY

The syndrome of vitamin K deficiency in man is characterized by bleeding into the skin (easy bruising and purpura) and from mucous membranes; hæmaturia is often the first signs of a bleeding state which soon becomes generalized. A latent bleeding tendency cannot be detected by the tourniquet test (Hess's test), which is normal in vitamin K deficiency, nor is the 'needle-puncture' hæmatoma a reliable sign of hypoprothrombinæmia.

The simplest index of the prothrombin activity in blood is the one-stage method of Quick. Tissue extract and calcium are added in optimum amounts to plasma (containing fibrinogen and prothrombin) and the clotting time of the mixture is measured to the nearest second. According to classic theory the speed of thrombin formation in such a mixture depends upon the concentration of prothrombin in the solution and therefore the clotting time of the mixture (the one-stage prothrombin time) will be a measure of prothrombin activity. It is now known that the one-stage prothrombin time depends upon the plasma concentrations of other clotting factors in addition to prothrombin. With the exception of factor V, however, these other factors also require vitamin K for their formation so that this test remains a most useful guide to vitamin K deficiency. It is simple to carry out and suitable for clinical use because it satisfactorily indicates the degree of coagulative abnormality and the probable tendency of a patient to bleed. It is essential that a parallel determination be made on normal plasma to act as a control.

The results of this test may be expressed in a number of ways.

(1) As a prothrombin time (16 seconds) compared with the normal control (12 seconds).

(2) As a 'prothrombin index': $$\frac{\text{Prothrombin time of control} \times 100}{\text{Prothrombin time of patient}}$$

$$\text{i.e.} \quad \frac{12 \times 100}{16} = 75 \text{ per cent.}$$

This index, though in common use, is misleading because it suggests that the patient's blood contains 75 per cent. of the normal concentration of prothrombin.

(3) As a 'prothrombin ratio': $$\frac{\text{Prothrombin time of patient}}{\text{Prothrombin time of control}}$$

$$\text{i.e.} \quad \frac{16}{12} = 1.3$$

This is a satisfactory and useful method of expressing prothrombin activity. It is a valuable guide to the dosage of anticoagulant drugs which should be adjusted so that the ratio lies between 2 and 2.5. Bleeding is likely to occur if the ratio exceeds 3.

There is a number of factors that, acting alone or together, can lead to a conditioned deficiency of vitamin K.

DEFECTIVE ABSORPTION

The body is solely dependent upon the amount of vitamin K absorbed from the alimentary tract. This may be insufficient to meet the need when there is chronic diarrhœa, for example in ulcerative colitis, or in steatorrhœa where, along with other fat-soluble vitamins, abnormal amounts of vitamin K are lost in the fæces. The habitual ingestion of large amounts of liquid paraffin may also lead to excessive loss of vitamin K. A somewhat prolonged prothrombin time can sometimes be demonstrated in all these circumstances (for example in some 20 to 30 per cent. in one series of patients with ulcerative colitis) but bleeding is unusual. A prolonged prothrombin time has also been reported in patients with peptic ulcer. The test might well be done in patients with peptic ulcer whose hæmorrhage does not soon stop after admission to hospital, when a prolonged prothrombin time should be taken as an indication to give vitamin K.

The most common circumstance in which there is defective absorption of the vitamin, however, is obstructive jaundice from any cause. This is important because a proportion of such patients will require surgical operation and bleeding may occur from the site of operation, and from other sites, usually within four days after operation though exceptionally up to the tenth postoperative day. Local bleeding, sometimes serious, may also follow needle-puncture biopsy of the liver in such patients. A normal prothrombin time (one-stage) is not necessarily a guarantee that bleeding will not occur following operation or biopsy and it is therefore wise to give vitamin K parenterally in doses of 5 to 10 mg. a day for three days before operation and for three to four days afterwards.

IMPAIRED SYNTHESIS OF PROTHROMBIN IN THE LIVER

Even when vitamin K is absorbed from the alimentary tract in amounts normally sufficient to permit adequate synthesis of prothrombin (and other factors) in the liver, however, the prothrombin time may be prolonged, and occasionally a bleeding state may occur, because of impaired production of prothrombin by the liver whose synthetic powers have been damaged by disease. In other words, an estimation of the prothrombin time (by the one-stage technique) is of no value in the differential diagnosis of obstructive jaundice from hepato-cellular disease. The response to injection of vitamin K, however, may be different, for in obstructive jaundice the prothrombin time can be shortened whereas in severe hepato-cellular damage it usually cannot be. Although the prothrombin time may remain normal when there is extensive liver disease, when it is abnormally prolonged it may be concluded that severe liver damage is present and the prognosis poor. Even in these circumstances, vitamin K should be given by injection since the prothrombin time may thus be shortened and bleeding from this cause prevented or corrected. It is worth while, too, continuing daily injections over a period

of ten to fourteen days since occasionally the response, unlike that occurring in obstructive jaundice, may be gradual.

DEFECTIVE SYNTHESIS IN INTESTINE

Since the vitamin K synthesized by the intestinal flora forms an important part of the daily requirements, it is not surprising that low prothrombin levels and bleeding have occasionally been described in patients on prolonged treatment with sulphonamides, though apparently not yet with antibiotics. These should be readily prevented or corrected by the administration of vitamin K preparations by mouth.

HÆMORRHAGIC DISEASE OF THE NEWBORN

This is characterized by bleeding from the umbilicus, together with dramatic hæmaturia, hæmatemesis and melæna occurring suddenly within the first five or six days after birth. The one-stage prothrombin time is prolonged but the disorder is not a simple one in which prothrombin only is involved. It can readily be cured or prevented by vitamin K. Defective synthesis of the vitamin in the infant's alimentary tract is believed to be an important cause, together with a low food intake, poor content of vitamin K in the milk, poor absorption of vitamin K from the alimentary tract and defective synthesis of prothrombin in the liver. It has been reported as occurring in as many as 1 in 200 to 400 of all live births and, whilst these may be maximum figures, it is more likely to be met with in premature than in full-term infants. Since vitamin K passes rapidly through the placenta, hæmorrhagic disease of the newborn can be prevented by giving the mother a single injection of 10 mg. early in labour. If that has been impossible, it is probably wise to give a premature infant a single injection of 2.5 mg. of a water-soluble preparation as soon as possible after birth. It has been reported, however, that excessive dosage with vitamin K is associated with a higher incidence of icterus neonatorum (and kernicterus). On the evidence available it would seem that smaller doses of vitamin K than those customarily given would be adequate and might be safer.

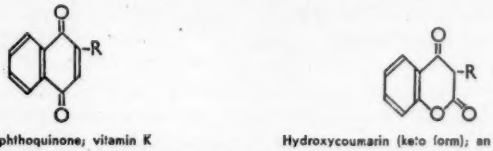
OTHER BLEEDING DISEASES

Idiopathic hypoprothrombinæmia is a rare disorder sometimes congenital, sometimes acquired, which is not solely the result of a low plasma prothrombin concentration. It is mentioned here only because the administration of vitamin K, though often disappointing, has led in some patients to a reduction in prothrombin time.

Vitamin K is of no value in the treatment of bleeding disorders unaccompanied by a prolongation of the prothrombin time. The hæmorrhagic manifestations of uræmia, however, are sometimes accompanied by a prolonged prothrombin time, possibly in some 20 to 30 per cent. of patients for reasons that are so far unknown. The parenteral administration of vitamin K is then indicated and is sometimes effective in controlling bleeding.

VITAMIN K ANTAGONISTS

Dicoumarol is a substance present in spoiled sweet clover which produces hypoprothrombinæmia and a hæmorrhagic disease in cattle which feed on the clover. The administration of anticoagulants related to dicoumarol and phenindione has been shown to be of value in the treatment of coronary thrombosis and myocardial infarction and the use of such drugs is gradually being extended into the field of prophylaxis. These substances produce hypoprothrombinæmia in man and may even cause bleeding, usually first manifest as hæmaturia. The abnormality is rapidly corrected by fat-soluble vitamin K_1. It therefore closely resembles the hypoprothrombinæmia of vitamin K deficiency and it is now considered that the coumarin group of drugs interferes with the synthesis of prothrombin (and factor VII) in the liver by competing with vitamin K for the prosthetic group of an enzyme system required for the rapid synthesis of prothrombin (fig. 2).



1:4-naphthoquinone; vitamin K Hydroxycoumarin (keto form); an anticoagulant

FIG. 2.—Structural formulæ of vitamin K and a vitamin K antagonist.

In the event of overdosage with a drug of the coumarin group (including derivatives of phenylindanedione), 100 to 200 mg. of vitamin K_1 should be given parenterally or by mouth. The synthetic water-soluble analogues are much less effective for this purpose and should not be used to counteract overdosage with a dicoumarol anticoagulant. An injection of vitamin K_1 will not restore the prothrombin level to normal for some eight to twelve hours. Blood transfusion is the only way of doing this quickly, although the shortening of the prothrombin time that follows transfusion is often disappointingly slight and transient.

Aspirin and salicylates also interfere with the synthesis of prothrombin. Diminished prothrombin levels have been found in patients taking such drugs over long periods of time, for example large doses of PAS during the treatment of tuberculosis, but the development of an overt bleeding tendency is uncommon.

CONCLUSION

This brief review emphasizes the limited but important role of vitamin K in clinical medicine. When it occurs, the deficiency syndrome is the result of one or more conditioning factors rather than due to dietary deficiency.

Vitamin K is especially useful in the prevention of hæmorrhagic disease of the newborn or its treatment and in the management of patients with obstructive jaundice with a prolonged one-stage prothrombin time or before and after surgical operation.

For the hæmorrhagic state that is produced by overdosage with a vitamin K antagonist (anticoagulant) large doses of vitamin K_1 are required.

THE USE AND ABUSE OF MULTIVITAMIN PREPARATIONS

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It will be convenient, and in accordance with accepted practice, to regard multivitamin preparations as those containing more than two of these substances. A combination of only two, such as the fat-soluble vitamins A and D or the water-soluble vitamins B and C is a rational association, for their absorption, storage and fate, and often their natural sources as well, are so alike that it is reasonable, economic, and proper to prescribe the two together, if a relatively cheap preparation containing both is available. Deficiency of water-soluble vitamins is encountered more often than deficiency of the fat-soluble substances, because stores of the former in the body tissues are more readily depleted.

USE

The vitamin B complex is, of course, a collection of vitamins in itself. It is thus strictly a multivitamin preparation and where deficiency of, for instance, aneurine is recognized there can be no objection to the administration of the whole complex, for it is likely to be associated with deficiency of other members of this group, although the physiological significance of a number of the separate components still lacks verification. Here the decision whether to give one or other of the complex or the whole, must be governed by the nature, severity, and etiological purity of the signs of disease. For instance, if polyneuritis is unquestionably resulting from aneurine (thiamine) deficiency high dosage may be needed and more readily given by injection of the pure substance than by oral administration of the whole complex, although often both methods are employed simultaneously. It is in fact the recognition of the coincidental deficiency of water-soluble vitamins B and C which has led to the widespread use of highly concentrated 'parentrovite' which has the advantage that it may be given intravenously or intramuscularly.

Turning now to the multivitamin preparations, most of which contain at least A, B, C, and D, the main indications for these are lack of adequate intake or imperfect absorption. In terms of disease this may be stated as inanition, repeated vomiting, fad dieting, and chronic diarrhœa such as is sometimes encountered as a feature of the post-gastrectomy syndrome, and the state following extensive resection of the small intestine.

Chronic undernutrition is still encountered as a result of poverty, especially in the vagabonds of this country, but it is a much commoner sight in many areas of the world, notably in the Far East.

The faddist who, from religious persuasion, or a misguided allegiance to

the pseudoscientific quack, believes that health can be achieved only by dietetic means, is quite a common instance of vitamin-deficiency diseases. Such persons flourish both in the United States and in Britain and are most resistant to the rational therapy of well-balanced meals. They may, however, be persuaded to their advantage to take multivitamin preparations. The same applies to the emaciated female with anorexia nervosa, but as with food, so with vitamin capsules, the swallowing must be observed by the physician or a reliable nurse, for these patients are extremely cunning and will deceive us if they possibly can.

Protracted vomiting of pregnancy may lead to appreciable vitamin deficiency which may adversely affect the fœtus as well as the mother. If multivitamin preparations cannot be retained, and this is rare, at least the readily depleted, and therefore most frequently lacking, vitamins B and C can be administered by injection.

Illustrations of chronic diarrhœa calling for vitamin supplementation of diet are presented by (1) ulcerative colitis, in which deficiency of vitamins B, C, and K can often be demonstrated; (2) chronic diarrhœa following extensive resection of the ileum for Crohn's disease; (3) idiopathic steatorrhœa in which deficiency of vitamins A, D, and K is most likely to arise; and (4) intestinal hurry following gastrectomy.

Quite apart from frank illness with multiple deficiency signs, it must be remembered that some degree of vitamin deficit may arise in spite of a normally adequate diet in the young who are growing rapidly, in pregnancy, and in prolonged pyrexial illness. It also occurs in those who through ignorance, laziness, or poverty, exist very largely on carbohydrates; notably the lonely widow, or more so the abject widower. The need for a high supplement of vitamin B complex is particularly necessary in this group.

The use of multivitamin preparations is justified in the instances cited until such time as the cause of the deficiency has been eliminated and the evidence of deficiency removed. In short, once the need has been satisfied the continued administration of multivitamins as a habit—a very easily acquired one—should be resisted.

ABUSE

The abuse of multivitamin preparations is simply their administration when there is no recognizable indication for them. The public wrongly believe them to be tonics and demand their prescription. To blame our patients for this importuning would be unfair, considering the pressure of advertising directed at them to this end. Moreover, simply as tonics they may be thought to be as efficacious as many agents in this category. If it is simply an appetizer that is required a little practical advice or the suggestion of more homely, sometimes more acceptable and often less expensive, remedies can achieve equally good results.

Well-fed women commonly assert that winter is a drain on their vitality and that they must have vitamins. The doctor is often at a loss to know how to cope with feigned ill health and may in desperation turn to vitamins

to provide the necessary magic. They are, after all, so safe, but the expense to the taxpayer should be weighed against this.

In general practice, too, debility, fatigue, nervous exhaustion, lack of concentration and various other vague complaints are such common presenting symptoms. They also feature in many of the more profound psychoneurotic conditions. Occasionally, frank mental disease is the direct outcome of a vitamin deficiency, e.g. some cases of Korsakow's syndrome. Derangements of vitamin metabolism have also been detected by laboratory tests among a number of patients in psychiatric institutions, including those regularly taking barbiturates. But this conglomeration of disconnected evidence can be no sure ground for embarking on massive long-term and consequently expensive multivitamin therapy for every case of psychosis and less still, probably, for every mild neurotic with whom the doctor is confronted.

Specific vitamin lack is known to be present with changes in the mouth like stomatitis (nicotinic acid), glossitis (riboflavine) and gingivitis (ascorbic acid). Definitive therapy is then essential. On the other hand, to treat every person with a sore, or uncomfortable, mouth—often a protracted complaint, especially among middle-aged women—by giving multivitamins, sometimes year after year, can scarcely be condoned.

Hypochromic anæmia is by no means rare. It goes without saying that an adequate diagnosis is the first essential. When iron deficiency is the cause the response to simple, orally administered iron is nearly always salutary. In these circumstances there can be little reason to prescribe fancy iron preparations containing a host of vitamins as well, in the belief that success will be better or more readily attained thereby.

Many of the antibiotics, especially those of the so-called 'broad-spectrum' class that are given by mouth, set up severe, if not grave, gastro-intestinal reactions. A state of avitaminosis B may indeed ensue. This can be avoided by more discreet or restrained antibiotic therapy or corrected to some extent by giving vitamin B perparations. But to proceed without restraint with 'broad-spectrum' antibiotics, on the assumption that they are safe simply because they are prescribed with a multivitamin supplement, is surely an illogical practice.

Finally, the most monstrous waste of vitamins is illustrated by their widespread prescription to old men demanding aphrodisiacs. The claim for this action is as well-founded as that of powdered rhinoceros horn. If such aid is called for, a cheap inert substance should be given, for the effect, if any, depends upon faith.

CONCLUSION

Perhaps the time has come for discarding the term vitamins. They may be vital in some sense, but they are certainly not amines. We now know the nature of the chemical substances with which we are dealing and they should rightly be regarded as food factors, or sometimes as drugs, and treated with scientific respect.

RECENT CHANGES IN THE CARE OF THE NEWBORN

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MUCH routine neonatal care is based on the common-sense idea that the physiology and the pathology of the new-born baby is general human physiology and pathology. But these differ just as much as appearance and behaviour differ between fœtus and newborn, newborn and infant. Only when this is fully realized, when false assumptions and analogies are discarded, and the special nature of neonatal physiology and pathology is understood, can progress towards rational treatment be made.

RESUSCITATION

Two good illustrations come to mind. Many workers have favourite methods of resuscitation. All are based on the idea that the new-born baby needs oxygen urgently, that failure to establish immediate regular pulmonary respiration at birth is likely to be fatal to life or to the nerve cells in the brain, and that oxygen requirements are the same for the newborn as for adults. Swedish workers have recently shown that both mature and premature new-born babies can thrive in oxygen tensions of 15 per cent., the fœtal level (Sjörstedt and Rooth, 1957). Wilson and his colleagues (1948), at Ann Arbor, have for many years been studying anaerobic metabolism in the newborn, and have pointed out that glycolysis can proceed to the stage of pyruvic and lactic acids without oxygen. Only one-sixth of the potential energy is liberated, but the required energy could be generated by an increased consumption of glucose. Although in the newborn the blood hydrogen-ion concentration is normal (pH 7.4), the carbon dioxide content is low whilst inorganic and organic acids are increased. In older subjects this chemical situation would be diagnosed as a compensated metabolic acidosis but, to quote Wilson, 'a situation which is pathologic for older babies may be physiologically normal for newborn or premature infants'. If little is known about the normal biochemistry of the newborn, the responses to trauma, to infection and to failure of pulmonary ventilation provide even greater mysteries.

Rickham (1957) has recently published some studies on the changes 'we initiate in operating on the newborn', and has demonstrated the peculiarities and the peculiar needs of this kind of patient. If ever resuscitation is to advance from an empirical to a rational exercise, preconceived ideas must be shed and knowledge collected about who and what really need treatment. Meanwhile, clearing the airway, keeping the head low and giving nalorphine to combat maternally given morphine or pethidine seem the only safe non-controversial measures. Intragastric oxygen (Åkerren and Furstenberg,

1950), one-half to one litre of oxygen delivered through a double catheter introduced into the stomach, is safe, easy and gives clinical satisfaction. Physiologists claim that it cannot work, clinicians say that blue babies become pink, settle and often begin to breathe comfortably under the influence. No-one knows how it works.

'HYPERBILIRUBINÆMIA'

The second illustration is 'hyperbilirubinæmia'. Those of us who were brought up medically while icterus gravis neonatorum was a tragic unsolved mystery, have watched with pleasure the unravelling of the tangled tale.

Landsteiner and Wiener's (1940) demonstration of rhesus blood grouping; Levine's (Levine *et al.*, 1941) brilliant hypothesis of iso-agglutination of rhesus-negative mothers by their rhesus-positive fœtuses; Fisher's prophetic theory of three pairs of linked allelomorphs (Race, 1944), one of each of the three present in the Rh gene, to clarify a confused situation; Coombs' (Coombs *et al.*, 1945) test for sensitized red cells; Diamond's (1947) simplification of the exchange transfusion through the umbilical vein, and the patient work of many, especially of Mollison at Hammersmith and Walker in Newcastle: all these have brought hæmolytic disease of the newborn under control.

The present principles of management may be summarized thus: case finding of rhesus-negative mothers by antenatal tests of the mother's blood, with follow-up tests for antibodies, especially at and after the 32nd week; the delivery in hospital of all mothers with antibodies; immediate cord blood tests with a decision to exchange the blood at birth in all babies who are rhesus positive, Coombs' positive, and have hæmoglobin values below 105 per cent. Using a polyvinyl catheter, exchanging 80 ml. per pound body weight, watching carefully for tachypnœa, tachycardia and a rise in venous pressure, have made the method easy and fairly safe, although there is still a minimal mortality rate of 8 or 10 per cent. from the transfusion itself (Norman, 1957). With these advances the problem has shifted to the prevention of hydrops or stillbirth and attempts to cut short the fœtal stage of the disease. Induction where there is a bad family history or rising antibodies undoubtedly plays a part. This means attempts to prophesy that a baby is affected. Walker (1957), in Manchester, has studied the bilirubin levels in liquor amnii sampled at the 32nd week. At Queen Charlotte's Hospital this technique has not been found helpful. Premature rhesus babies as a group have higher birth weights than the babies of toxæmic mothers (Murray, 1957). But premature induction highlights the problems of hyperbilirubinæmia.

Without any hæmolysis or red-cell agglutination the normal breakdown of worn-out red cells liberates too much bilirubin to be metabolized by the new-born baby's liver. Simple or physiological jaundice results with serum-bilirubin levels rising to 12 or 15 mg. per cent. The rise is due to the failure of the liver to perform the double conjugation of bilirubin with glucuronic acid, which turns a fat-soluble material into one that is water-soluble and excretable in fæces and urine. The conjugation becomes effective and lowers the serum-bilirubin level between three and eight days after birth. In the

interval, should the level be high, especially as the result of excessive breakdown of hæmoglobin from whatever cause, the danger exists of deposition of bilirubin in the tissues and in the brain cells where the resulting damage leads to kernicterus. Whilst hæmolytic disease is the commonest cause of dangerous hyperbilirubinæmia, premature babies, whose livers, as Professor Lathe (1955) has taught us at Queen Charlotte's Hospital, take longer to develop the power to conjugate bilirubin, are also at risk. There is still difference of opinion about the exact indications for exchange. At Queen Charlotte's Hospital, with the current laboratory methods all hæmolytic-disease babies are exchanged or re-exchanged when the unconjugated bilirubin level reaches 20 mg. per cent. (there is a 1 mg. error in both directions). This is only a potentially dangerous level but the rise may be extremely rapid (10 mg. per cent. in twelve hours). With premature babies the urgency is less and the decision depends upon the age and size of the baby, but 25 mg. per cent. on a rising curve would be the absolute upper limit. Kernicterus of prematurity undoubtedly occurs, but some of the diagnosed cases may well have had rising bilirubin levels as the result of undisclosed agglutinins and hæmolysins from AB incompatibilities. In the last four years since these methods were adopted no baby has been found to have kernicterus in either post-mortem room or follow-up clinic. Because of the dangers and complexities of hæmolytic disease and of its treatment, mothers at risk should, in my opinion, always be delivered in hospitals where sufficient numbers are treated to merit a twenty-four-hour pathology service and to develop familiarity with all the laboratory and clinical techniques required. We await an Ehrlich who will identify the missing liver enzyme and prepare it for use in the control of hyperbilirubinæmia.

INCUBATORS AND OXYGEN

Fashion has decreed a new look in the care of the premature baby—a look through the perspex of an incubator at the unclad specimen, at least for those weighing 3½ pounds (1.6 kg.) and less. To do the exact opposite in every detail of what was done to premature babies twenty years ago is a safe rule for the modern pædiatrician. The interest in gas and oxygen apparatus engendered by the 1939-45 War led to the use of oxygen in increasing numbers of new-born prematures. This in turn led to enclosing at least the face in apparatus which was elaborated from home-made cleaned x-ray plates joined together with sticking plaster to the complex temperature and humidity controlled oxygen apparatus of today. Twenty years ago incubators for babies were anathema (we had some in the basement at Queen Charlotte's) and then, through an entirely unscientific demand for high oxygen atmospheres, the babies were back in incubators once more—but with a great difference.

They were much more efficient, temperature and humidity could be accurately controlled, and (alas!) oxygen atmosphere could easily reach 70 or 80 per cent. There followed the outbreak of retrolental fibroplasia, which

for two or three years became the commonest cause of childhood blindness. Now the maximum oxygen allowed is 30 per cent. and this for the shortest time until respiration is properly established. Some think that the vascular changes stimulated by prolonged oxygen administration in small premature babies, that underlie the retinal separation of retrolental fibroplasia, can lead in the lungs to the deposition of hyaline membrane in the pulmonary alveolar ducts.

Strategic concern with thermodynamics and the prospect that some of the third world war may be fought out amid Arctic wastes have helped to stimulate renewed work on the effects of heat and cold. Hypothermia has already established itself in the operating theatre and is working its way into the premature unit. Incubator temperatures are creeping down from 95°F. to 85°F. (35°C. to 29.4°C.) and even lower. The diagnosis can now be made of the hibernating baby born with a rectal temperature of less than 90°F. (32.2°C.), with slow respiration, bradycardia and general peripheral cyanosis in grave danger from a too rapid warming. The increased metabolic and oxygen requirements may not be met and the baby may die, so that the temperature is coaxed up slowly over two or three days. The dangers of heat, and especially of rapid heating, are now recognized, as well as the dangers of exposure to cold after birth.

From birth, premature babies used to be fed milk and brandy through glass pipettes at half-hourly intervals; now they are left until they 'ask' for food. This system, satisfactory for those over $3\frac{1}{2}$ pounds (1.6 kg.), is not wise in those of lower weight. After the first twenty-four hours, a polyvinyl tube is passed into the stomach and the baby fed three-hourly through a syringe. Such a tube can stay in place for ten days or more until the baby is ready to suck from a spoon. Dehydration is prevented. The best feed is still breast milk for the first three weeks, a human milk bureau or bank being convenient for this work. Sometimes with slow weight gain this milk needs reinforcing with sugar, 30 grains (2 g,) rising to 60 grains (4 g.) to four ounces (115 g.) (8.5 to 10 per cent. sugar mixture). Should the mother fail to lactate the feed may then be slowly changed to a half-cream dried milk powder.

CARE OF THE CORD

The curious reversal of old-fashioned practice, which has led to postponing the first bath, has involved the care of the umbilical cord. Boracic powders date from the Listerian 'seventies, but binders from antiquity. About a decade ago binders went out of fashion, the whole cut cord was painted with collodion, then only the cut end was so painted and finally the cord was left unpainted and undressed. The experiment illustrated the general proposition that with normal babies any treatment succeeds unless and until it is put to the test. Experience eventually teaches the dangers of infection of the cord and leads to some protective treatment. What the treatment should be is beyond my powers to tell. The cord is readily colonized by bacteria, notably coagulase-positive staphylococci, a phenomenon prevented

by the daily application of Bonney's blue, gentian violet in spirit or chlorhexidine (1 per cent. in 60 per cent. alcohol). Such treatment seems to delay the separation of the cord: with Bonney's blue one cord separated on the fifty-sixth day. After a two-year flirtation with Lövset clips we have returned to linen thread.

OPHTHALMIA NEONATORUM

The prophylactic treatment of the conjunctiva at birth has been omitted after about a century. Each eye is swabbed with sterile water immediately after birth and no further treatment used unless there is conjunctivitis. Then a culture is made and sulphacetamide drops or an antibiotic ophthalmic ointment applied. With marked swelling and purulent discharge an antibiotic is given orally or parenterally as well. Treatment is adjusted in the light of the culture and sensitivity results. Whenever silver nitrate drops are discarded cases of gonorrhœal ophthalmia follow. At Queen Charlotte's there are one or two each year out of some 3000 live births, but all have virtually healed before the full laboratory report has become known. Under prevailing conditions the infection is quickly and easily controlled, there is no risk of blindness and the diagnosis in the baby leads to diagnosis of infection in the mother. These remarks apply only to those communities which organize the control of venereal disease. Public propaganda, special treatment centres, well-attended antenatal clinics, all play their part in the case. The infected mother who runs the gauntlet of this system and comes undiagnosed to the clean maternity hospital is rare in this country. And so long as this remains true the one last prophylactic measure may be safely omitted with a consequent reduction in sticky eyes from silver-nitrate irritation.

SOME OTHER DEVELOPMENTS

The care of the newborn, like other routine matters, always reflects fashion. Change depends on other and more scientific factors such as the recognition of a new type of pathological process, the establishment of a new diagnostic test, the elaboration of a new type of treatment, the discovery of a new kind of drug, further information about an old drug for good or ill.

All of these have contributed to changes in the management of hæmolytic disease of the newborn. The new type of pathological process was brought to light in the study of inexplicable blood transfusion reactions which led to the discovery of iso-immunization of the mother by her own fœtus. The new diagnostic tests are rhesus testing, antibody measurement, and of sensitization (Coombs' test). The new type of treatment is exchange transfusion, and we await the new drug, the missing enzyme. Meanwhile new knowledge about old drugs has taught us that the danger of hyperbilirubinæmia is increased by the use of vitamin K and sulphafurazole.

The enzyme deficiency in this case is temporary. Permanent enzyme deficiencies, inborn errors of metabolism, are being increasingly recognized. The immediate change has been to bring to the newborn the excellent

clinical habit of the routine urine test. The baby who fails to thrive at the end of the first week should have a urine test, not only for evidence of infection but for reducing substance. So will early cases of *galactosæmia* be diagnosed and the sad sequelæ of cataract, hepatic cirrhosis and mental defect be prevented by the use of a galactose- and lactose-free milk. Routine urine tests for phenylpyruvic acid may likewise rescue a child from the mental defect and epilepsy of *phenylpyruvic oligophrenia* (phenylketonuria) with the help of a phenylalanine-low diet (Woolf *et al.*, 1958). Doubtless more of these enzyme deficiencies will come to light in time, helped by the identification of intermediate products of metabolism, abnormal sugars and abnormal patterns of amino-acids by chromatography—the last an illustration of a new diagnostic test.

Another new test, equally dramatic but simpler, is the use of the plain abdominal x-ray in the diagnosis of *neonatal intestinal obstruction*. At birth the abdomen is dull to percussion and the airless gut is opaque to x-rays. Within six or eight hours swallowed air has travelled from stomach to rectum and an air bubble in the rectum should be seen in a picture after twenty-four hours. The absence of rectal air means an obstruction, so that any baby vomiting much, and especially vomiting chemically identified bile, should have a lateral abdominal x-ray. A hold-up of air should lead to laparotomy, although air can get through in some forms of secondary obstruction such as volvulus, in malrotation or in the functional obstruction of Hirschsprüng's disease.

The elaboration of a new kind of treatment as the impetus to change in care is well shown in *congenital heart disease*. I remember twenty-four years ago sitting in Dr. Helen Taussig's rheumatic clinic in the Harriet Lane Home, Baltimore, while she tried to put together what she called her jigsaw puzzles—cases of congenital heart disease, many sent mistakenly in those days as cases of rheumatic fever. At this time the expert on congenital heart disease was Dr. Maude Abbott in Montreal, a morbid anatomist who collected hearts. With the rise of cardiac surgery the old 'laissez-faire' or 'laissez-mourir' attitude has departed. Heart failure in the newborn can be recognized and should always be treated, using rest, oxygen, digoxin with a digitalizing dose over 36 hours of 0.04 mg. per lb. (0.09 mg. per kg.) body weight, and morphine 1/600 grain (0.1 mg.) per lb. (0.22 mg. per kg.) per day as required. An abnormal heart that was good enough for the fœtus and can be good enough for the infant may fail during the circulatory adjustments that follow birth. Medical treatment may permit survival through the period of danger, leaving the hope of compensation or of surgical relief in the future. I do not yet favour neonatal diagnosis by angiogram or catheter.

The most important new kind of drug is without doubt the antibiotic. *Chemotherapy* up to the time of the sulphonamides made little difference to the prognosis of infection in the newborn, which used to be the commonest cause of death after the first three days. There were two kinds of cases:

those who died and those who, remarkably, survived. The first help came from penicillin in the treatment of staphylococcal disease. But the staphylococcus became resistant and the second commonest pathogen, *E. coli*, was never very sensitive. Streptomycin came to the help of penicillin, but perhaps to be preferred is the wide-spectrum antibiotic. We do not, at Queen Charlotte's Hospital, use prophylactic skin antibiotics lest we encourage sensitization in the babies and resistance in the bacteria, but we do use antibiotics without bacterial diagnosis in non-thriving babies suspected of septicæmia and to prevent bacterial pneumonia in babies who have greatly inhaled at birth or who have been difficult to resuscitate. Bacterial pneumonia has become a rare finding in the post-mortem room.

BCG inoculation is recommended when there is any risk that active tuberculosis might develop in the home. Complete separation from a mother known to be actively tuberculous is still considered wise.

Steroid therapy has not yet found its place in the new-born nursery. All I can say from personal experience is that prednisolone can raise the platelet count in neonatal idiopathic thrombocytopenic purpura.

SUMMARY

In the last ten years advance has been rapid. The total neonatal mortality rate of 20 per 1000 live births in 1949 had almost halved by 1953. And the premature mortality rate dropped in the same period from 18.3 per cent. to 9.3 per cent. Infection rate and morbidity rate have dropped dramatically. The next step is to establish chemical and endocrine correlations with clinical problems so that clinical diagnoses become more accurate and reveal what really needs treatment. Diagnoses like asphyxia neonatorum, the cerebral baby, hæmorrhagic disease of the newborn, belong to the medicine of our ancestors.

Whatever methods result, it must be remembered—and this is always the pædiatrician's epilogue—that the pædiatrician like the mother and the baby is in the hands of the obstetrician. The fundamental need is for the best possible, and the fullest possible, obstetrical care—antenatal and in the labour ward. By comparison with this, all the care and the skill of the pædiatrician is as nothing.

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THE JAMES MACKENZIE LECTURE

THE ART OF CONSULTATION*

By G. F. ABERCROMBIE, V.R.D., M.D.
*London, N.W.*3

IT is one of my life-long regrets that I never had an opportunity to meet Sir James Mackenzie. When I went into practice in 1924, I bought a copy of his little book, 'Principles of Diagnosis and Treatment in Heart Affections', and was as at once spellbound. What an enormous influence that book must have had on all the young men who studied it—with its brilliant differentiation of cardiac irregularities, and its insistence on the efficiency or failure of the heart muscle, but I was also fascinated by his analysis of what nowadays is called clinical instinct.

'A thing that strikes anyone', he says, in his other book 'The Future of Medicine', 'is the curious knowledge which some physicians and general practitioners acquire after many years' practice. The knowledge is indefinable, and they are unable to express the reasons in language sufficiently clear for the uninitiated to understand. The real source of this knowledge is the familiarity, derived from experience, of the appearance of the patient when stricken with an insidious disease, a subtle alteration in the expression of the face, or a slight wasting, or a faint contraction of some of the muscles of expression; a faint change in colour, coupled, it may be, with an alteration in the patient's temper, ideas or voice. Knowing the patient before these changes occurred, the attention is arrested by the alteration'.

Let us go a little further back for an illustration of what Mackenzie had in mind, and for a good description of a consultation.

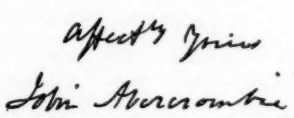
'We remember', says Dr. John Brown of Edinburgh in a famous essay, 'hearing a young doctor relate how, on one occasion when a student, he met with the late Dr. Abercrombie, when visiting a man who was labouring under what was considered malignant disease of the stomach. He was present when that excellent man [this must have been about 1840] first saw the patient along with his regular attendant. The doctor walked into the room in his odd, rapid, indifferent way, which many must recollect; scrutinized all the curiosities on the mantelpiece; and then, as if by chance, found himself at his patient's bedside; but when there his eye settled upon him intensely; his whole mind was busily at work. He asked a few plain questions; spoke with great kindness, but briefly; and, coming back to consult, he said, to the astonishment of the surgeon and the young student, "The mischief is all in the brain, the stomach is affected merely through it. The case will do no good; he will get blind and convulsed, and die". He then in his considerate, simple way, went over what might be done to palliate suffering and prolong life. He was right. The man died as he said, and on examination the brain was found softened, the stomach sound.

'The young student, who was intimate with Dr. Abercrombie, ventured to ask him what it was in the look of the man that made him know at once. "I can't tell you, I can hardly tell myself; but I rest with confidence upon the exactness and honesty of my past observations. I remember the result, and act upon it; but I can't put you, or, without infinite trouble, myself, in possession of all the steps". "But would it not be a great saving if you could tell others?" said the young doctor. "*It would be no such thing; it would be the worst thing that could happen to you;* you

* The fifth James Mackenzie Lecture, delivered before the College of General Practitioners on November 22, 1958.

would not know how to use it". "Was it something in the eye?" said his inveterate querist. "Perhaps it was", he said good-naturedly; "but don't you go and blister every man's occiput, whose eyes are, as you think, like his" '.

The passage from Sir James Mackenzie, which I have quoted, and the description of my first cousin, many times removed, stimulated me to read again all the consultant opinions recorded in my notes—notes which were invariably written on the same day as the opinions were expressed—and my general theme will be that the family doctor must learn to manage, not only the patient and his relations and friends, but upon occasion his specialist colleagues also. In other words, he must remain in charge and in control unless, with the patient's consent, he delegates his authority to another, temporarily and for some special purpose.



A STROLL DOWN HARLEY STREET

Let us then take a stroll together down Harley Street, using that term generically. This will be no scientific expedition; I shall not analyse or classify; nor shall I introduce to you by name those whom we happen to meet. We must not spend long with the eccentrics, who assure us that the water in the Lake District is the best for treating a London boy's eczema, or who recommend for boils a course of treacle enemas, specifying particularly Fowler's West Indian. We shall listen respectfully when the talk is of Pancoast's syndrome or Schimmelbusch's disease, but we shall not be impressed by statisticians. As a family doctor, I am not concerned with percentages, but only with people, with men, women and children, individuals, one at a time. The average expectation of life without operation may be so and so, the mortality of the operation such and such, but that is not the point. The point is what will happen to this, to *my*, patient. How one's heart still warms to the surgeon who won't operate!

'I'm afraid from the surgical point of view, it is rather a dud. His epilepsy is pretty generalized and there is no suggestion of localization. It is the most hopeless kind. Of course, *any* operation benefits epilepsy for a time, and one must be scrupulously careful in advising it. A case could be made out, but all my judgment is dead against it. He needs a dull mechanical job'.

We shall take kindly to the surgeon who said: 'It *is* rather a good idea to regard the husband as one of the physical signs'; and to the physician who wrote: 'But you know her better than I do, and if you have any other view, I hope you will let me know'. Someone may stop us in our walk to ask how that patient, whom we saw together, fared, and I shall be very happy to tell him; but I have never felt that it was any part of my duty to ***write*** to a consultant and tell him he was wrong. I was once tempted to write to an old friend that he had missed a cancer, but I refrained, and I am glad of it, for, within a week, and quite unknown to me, he died of that disease himself.

The evolution of the doctor in the suburb, and particularly in the London suburb, follows a quite different course from that of the doctor in the country, so well described to us by my predecessor last year. I soon found, when I joined my partner more than thirty years ago, that, although I was reasonably well trained to do certain things, I was not going to be allowed to do them. My partner was an elderly and experienced man, and his large practice consisted mainly of well-to-do people, many of whom came up from the country to be under his care. Both he and they were perfectly clear as to what was required in serious illness or accident—the best possible advice and treatment. My chance therefore of removing their appendices or their children's tonsils was never good, and soon disappeared altogether. In its place, I was offered unrivalled opportunities for the study of the art of consultation.

When my partner went on holiday that first summer, he left in my care a girl of 19, who appeared to be recovering from a small pleural effusion, and from her parents I learnt the first lesson of all: namely, that he who pays the piper calls the tune. They indicated, with a tact and charm which I have not seen equalled, for they were Americans, that they would like a consulting physician to see their daughter, with me, every day, and thus in quite a short time I became familiar with the ceremonial. When that physician went on his holiday, he was replaced by another, and he, in his turn, by a third. Meanwhile, a pathologist, a radiologist, an anæsthetist and two surgeons had consulted about her with me. In the middle of her illness, which lasted about six weeks, a thoracotomy was done, but still her temperature remained unsettled. At last, and quite abruptly, it fell to normal, and I shall never forget the smile of satisfaction which spread over the face of the third consulting physician, as he beheld her chart on that eventful morning. 'There now', he said, 'you see, if we had done anything . . . but we haven't'!

THE ART OF SELECTION

The art of consultation was not then, and it should not be now, simply a question of sending a patient away for a second opinion; it is the careful selection of the man who, by training and by temperament, is the most suitable for the matter in hand. His position in the profession, his standing in his specialty, his skill, his appearance, his manner, and his gift of tongues have all to be considered. We knew our men pretty well for we met them in person at every opportunity. The field of choice was very wide indeed, limited only perhaps by something in the patient's past history. This, too, might be quite extensive. I remember seeing a lady, who had obviously been

very ill, and who informed me that I was the twenty-ninth doctor she had seen.

My partner made it perfectly plain to all his patients that, if they wished, a consultation would immediately be arranged, but also that, if he himself felt the need of a second opinion, no objection should be offered. The patient often requested that a particular individual be summoned, someone perhaps who had operated on another member of the family, or who had given sound advice on a previous occasion; and this request, unless absolutely unsuitable, was invariably granted.

A FIRST PRINCIPLE

In this way, I met many physicians and surgeons from hospitals other than my own, and I learned a great deal from them, but it was my own surgical master, Sir Holburt Waring, who taught me, in a single word, one of the fundamental principles of consultation. Quite recently, I had been his house surgeon, and, as was his custom, he seemed to view my early efforts to assist him with a tolerant, even a benevolent amusement, but after ten days —puppies should have their eyes open on the tenth day, should they not?— the rains descended and the winds blew and beat upon that house surgeon, culminating in his classic denunciation: 'Really, Abercrombie, you are the worst house surgeon I've ever had!' This formidable being, white-haired and gruff, was called in consultation by my partner, when I had been with him only a month or two, and as always I was bidden to attend. In giving his opinion, he turned to me and said: 'I think, Dr. Abercrombie, if you will do so and so . . .'. DOCTOR Abercrombie! Had he really said 'Doctor'? He had! By that single word, by that title, he acknowledged, indeed he welcomed, me as his colleague, and made it clear that at last we met on level terms. That is as it should be. When a consultant and a general practitioner meet, no matter how distinguished the one or how obscure or diffident the other, they meet on terms of absolute equality, the one to give, the other to receive, but not necessarily to adopt, the advice tendered. The consultant must be careful here. He should be patient while the practitioner tells his tale; he should not wave away, as of no account, the x-rays that have been brought; and he should not, with a brisk 'Well, I don't think we need discuss this together, need we?' deprive the practitioner of the opportunity to consider what is to be said to the patient, before it *is* said.

It is beyond all doubt that a consultation between two men from the two different worlds of medicine—one, as Keevil put it, from the Ivory Tower of the operating theatre, the other from the Augean Stables of first-aid—is of immense value to the latter, for it affords him priceless opportunities of keeping up-to-date. 'Will you demonstrate this case to me?' said I. 'Do you mean that?' said he, 'We neurologists love showing off'. But a very close association with Harley Street is not altogether a good thing, for it may sap a man's confidence and gradually destroy his self-reliance. I have known men become so fearful of responsibility that they would not even

give gas for an ordinary dental extraction. But consider another simple situation.

I am summoned at one o'clock in the morning to find, in a small top-floor flat, a young woman with a deep sliced zig-zag gash in the face, starting below the eye and ending near the mouth. Now I know well that my friend the plastic surgeon, with his anæsthetist and his assistant, his theatre and his electric sucker, will make a perfect job of this; and I expect that the house surgeon in the near-by hospital, with the night nurse to help him, will do it pretty well too; but I also know that, for the good of my soul, and despite my remarkably improbable aseptic technique at that hour of the morning, I *ought* to do it, and I can only hope and pray that antibiotics are as good as their reputation.

THE INFORMATORY CONSULTATION

Consultations are arranged, generally speaking, either for information or for action; often of course for both purposes. Let me give a few examples of the first, the informatory, often the reassuring.

A girl, aged 18 months, pulled a kerosene lamp off a table and burned the left side of her face. Her parents were desperately anxious lest the eye should have been damaged. A little later, the surgeon gives his verdict. 'The eye is undamaged, because the reflex is invariably quick enough to protect. This child is now without pain, and there is no spasm of the eyelids. If an eye is burned, pain is agonizing and spasm invariable'.

A small boy has a severe attack of measles. His mother nurses him in her arms day after day, and he gets well. Ten days later his temperature rises to 102°F., and I am disturbed by some evident stiffness of the back, and by the complete absence of other signs. A physician, finding neither drowsiness nor irritability, is satisfied that it is only influenza, and does not advise either chemotherapy or lumbar puncture.

The parents of an eight-year-old boy ring me up from the seaside to say that 'the light seems too strong' for his eyes. This is an odd story. We are all familiar with the glare from the snow in the Alps or from the sea in mid-Atlantic, but that the light in an ordinary English seaside resort should be too strong for the eyes of a healthy little boy is something quite outside my experience. Should they bring him up to London? Well, yes, I think they should. When he arrived, I found he had a squint, and an eye specialist, finding in addition some swelling of the optic disc on both sides, feared a cerebral tumour. A neurologist confirmed this diagnosis in a matter of seconds. He simply drew the boy towards him and tapped his skull with a finger, and the skull was toneless, cracked, sprung unmistakably. Now if only I had thought of doing that, I could have made the diagnosis as well as he. I am never likely to hear that sound again, tap I never so many small boys' skulls.

These men gave their opinions with absolute assurance. I may have had an idea, but their reasons were so convincing that they converted the idea into a certainty.

Here is another first-class opinion. This lady was in the grip of a severe toxæmia of pregnancy, and the position and the prognosis were thus presented.

'After a fortnight's rigorous treatment, she has really made very little improvement, and such cases must always be regarded with great respect. At any moment very serious symptoms may supervene—boring headache, repeated vomiting, fits —which will certainly alter the clinical picture. The pregnancy ought to be ter-

minated. The child seems very small for its maturity and probably there is already some placental infarction. These children tend to die *in utero*; if the pregnancy continues this will almost certainly happen, and it is a big risk to take for a very remote chance of a satisfactory baby. If interrupted now, there will be no permanent kidney damage, and future pregnancies should be perfectly normal'.

Often, of course, one gets no help at all.

An elderly man, who had suffered much from bronchitis and emphysema in the last ten years, called me one evening on account of substernal pain. His condition deteriorated and I went to see him again just before midnight; a short cough was a pronounced feature, there were some moist sounds at both bases, his abdomen was distended, and he was dyspnœic—systolic pressure 170, pulse 120. I called a physician, who took the view that he had a small pneumothorax on the left side, and, having sent for an oxygen apparatus and a nurse, we went to explain the situation to the family. Being a little unhappy that the patient should thus be left alone, I soon slipped away and went back into his room. He was sitting up in bed and looked rather better, and we talked about his treatment and the nurse, who was to come. 'Now', he said, tapping the midline of his chest with the tips of his fingers, 'this pain is coming on again', and he hitched himself up in bed. He put out his right hand for me to help him, and as I took it, his breathing became stertorous, his face turned blue, his head went back, and his pupils dilated. He was pulseless, and after a few laboured, rather desperate, inspirations, he died. An examination revealed exactly what we thought it might—a spontaneous rupture of the heart at the site of an infarct, for the pericardium was full of soft blood clot and there was a jagged tear, an inch and three-quarters long, in the left ventricle.

I would not have you think that I here intend criticism of a consultant opinion; I only wish to stress that it is no part of the art of consultation to leave, unattended and alone, a man who may be on the very brink of death.

A boy weighed 8½ pounds at birth and labour was normal. At three months he weighed just under 11 pounds, and had gained only 9 ounces in the last five weeks. He was pale, very pale, and panted in a curious way. I have never before or since seen a baby pant. I took a pædiatrician to see him who, finding no disease, suggested he was an air-swallower. He made some small alterations in diet and prescribed something for wind. Two days later, quite suddenly, the boy died, and the necropsy revealed a very pronounced aortic stenosis.

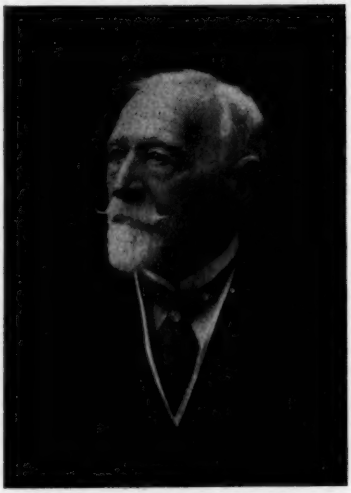
Harley Street, in my experience, is reluctant to confess itself stumped. It would be better sometimes if it did, and the exceptions are refreshing. 'Your doctor has called me', said another pædiatrician one night, 'because he cannot put his finger on the exact cause of this trouble, and I am in the same position. We ought to take this boy into hospital and investigate the urine, the cerebrospinal fluid and so on'. When we left the house, he paid me a handsome compliment. 'There are black spots in my practice, Abercrombie, and you are one of them. I always know that, if you can't make a diagnosis, I shan't be able to make one either'.

THE PROBLEM OF CANCER

A lady was thought to have a lump in the breast, and because it happened to be convenient, a consultation was arranged in the family doctor's house.

The surgeon examined her very carefully, but found nothing, and crossed the room to wash his hands. After a moment or two, he laid aside the towel, and returned to examine the patient again. He then found what the practitioner had called him to see, and he confessed afterwards that he could not escape the conviction, that he would not have been summoned unless there *was* something.

These cases are always distressing for, if at all possible, a mutilating operation there must be. The question is 'How much?' and the practitioner will know his surgeons well enough to be able to forecast what operation any one of them will recommend in any particular case. His responsibility is not lessened, but rather increased thereby. At any moment now, it seems to me, some pharmaceutical firm will announce a new drug for the treatment of cancer, and if the history of antibiotics and of tranquillizers is any guide, that announcement will be followed within a matter of months by a dozen such discoveries. Our College will then have an immense opportunity if we are but ready for it. Have we a plan for the immediate investigation of such new remedies? Our new building, to which we all so keenly look forward, is to be alongside the Royal College of Surgeons and the Imperial Cancer Research Fund. We ought now, in anticipation of something revolutionary in the treatment of cancer, to have a consultation with those bodies, and prepare a scheme to assess the value of a new therapy. I suppose each one of us in this College, each family doctor, will see at least ten or a dozen new cases of cancer every year—say thirty or forty thousand cases annually in this country alone. What a wonderful opportunity there may be, if only we are ready to seize it!



Aug 3. 1919. Clifford Allbutt

A FUNDAMENTAL PRINCIPLE

'If I had my way', said Sir Clifford Allbutt as long ago as 1889, 'no man should die of acute or obscure disease without a consultation'. You notice he does not say 'without a second opinion'; he says 'without a consultation'. This, surely, is a right and fundamental principle in the practice of medicine. From time to time we all see exceedingly rare conditions, of which we have had no previous experience—so rare, perhaps, that even the specialist we propose to call has never seen such a thing before. Even so, and no matter how confident we may be that we have arrived at the correct diagnosis and have instituted the best possible treatment ourselves, we should always hold to the principle that no man should be allowed to die of acute or obscure disease without the benefit of a consultation. And Allbutt, whose regard

Sir James Mackenzie especially valued, goes on to say, to the students at Charing Cross Hospital:

'It is you touchy young men, just out of the schools, who give us the trouble—who bridle up at the suggestion of a consultation and declare that nothing more can be done. An older man knows that a good talk over a case is, at any rate, a pleasant meeting, and probably valuable to him at least in bringing about an orderly revision of the symptoms, and in refreshing the confidence of his patient. He knows, too, that when a doctor is sick himself he calls out for a consultation sooner than a layman does, and runs from one doctor to another in defiance of all convention. I never knew a sick doctor who failed to consult at least three London physicians in a forenoon, usually concealing from each his visits to the others. The fact is', he concludes, 'life is dear not to doctors only; to me it is marvellous, not that patients slip off to consultants, but that, with the fear of death before them, they are so loyal to their own advisers'.

A HIDDEN SNAG

There is a hidden snag about a consultation to elucidate a diagnosis. It happens now and again that a change occurs in our patient's condition in the interval between our last visit to him and the arrival of the Great Man. A gland may have appeared above the left clavicle, a patch of bronchial breathing, a rash, some free fluid in the abdomen. The Great Man, confound him, pounces upon this instantly! It is obviously the solution to the enigma, and we look foolish because we have not spotted it ourselves. We can prevent that by following the wise advice of an old family doctor, whose name, to my sorrow, I cannot trace: 'I made it a rule', he said, 'always to re-examine my patient on the morning of a consultation'. If we get there five minutes early, we can have a quick look round, and save ourselves a good deal of irritation and embarrassment.

ON CHANGING CONSULTANTS

When a general practitioner summons a consultant for action, the circumstances may be very dramatic indeed, and he must be free, and indeed may feel compelled, to chop horses in midstream.

A handsome youth had been ill for ten days and was brought up from the country to a small nursing home with high fever and a brawny swelling on the left side of the neck. Under an anæsthetic, a surgeon made a small incision into this, without finding pus. The fauces were carefully palpated, but as nothing abnormal was found, a tube was placed to drain the wound and fomentations were applied. Late next day I was summoned very urgently, and found him receiving oxygen, his temperature 103.6°F., pulse 120. He was pale, sweating, very anxious, and drew breath with great difficulty and loud stridor. By dint of strenuous exertion, he managed to cough up some sticky mucus, and by degrees the spasm passed; but he sat a long time bolt upright, with head thrown back and eyes staring, chin pushed forward and the angles of the mouth drawn down, before he was able to breathe quietly.

Ignorant of the cause of this condition, the like of which I had never seen before, I drove down to Harley Street and dragged a throat specialist from his Christmas dinner. This man glanced at the larynx and said 'œdema'. He told us how suddenly the glottis might be entirely occluded and breathing cease. Tracheotomy, he went on, had a mortality of 50 per cent.; intubation, though easy, gave even worse results, for at any moment the tube might be coughed out. He believed there was

an abscess somewhere in the neck, and we must try to open it under local anæsthesia, for a general anæsthetic would be fatal. The boy's father, in traditional phrase, 'put himself in our hands'. 'That's right', said the surgeon, 'that's all you *can* do'. 'Novocaine' was injected deeply in various directions and the wound enlarged and explored. This provoked an alarming attack of dyspnœa and the surgeon waited quietly for twenty minutes. At length, by a finger behind the sternomastoid, two or three ounces of thick pus were evacuated from a retropharyngeal abscess, and an hour and a half later, respiration was a little less laboured. He had his ups and downs, but in a month he had recovered.

Twenty years later, I met him. 'You don't remember me', he said, 'but perhaps you recognize this', and he pointed to his scar. Oh, yes, I recognized that, and we both remembered with gratitude and glass in hand the man who made it.

YESTERDAY AND TODAY

Strange to think that today the whole thing would have been scotched by a prompt and determined use of modern drugs, but modern investigations are not an unmixed blessing, and we sometimes see our specialist colleagues hypnotized by them. A physician has even refused to see a child patient with me outside his hospital, for fear that his opinion would be valueless before she was 'investigated'.

In 1938, I saw a two-year-old boy in evident abdominal pain. The spasms occurred at intervals of perhaps five or ten minutes, and then he cried a little, lifted his legs off the bed, and folded them over his abdomen. He scratched at his navel with his fingernails, and during one of these spasms, some blood-stained serum passed through the anus. The diagnosis was intussusception, and the pre-war surgeon agreed without hesitation. 'After all', he remarked, 'it can hardly be anything else, as there is *NO* diarrhœa', and he operated there and then.

In 1956, I saw a precisely similar condition in a boy aged five months, and discussed it with a post-war surgeon. Now he did *not* say, 'It can hardly be anything else, as there is no diarrhœa', he said, 'They get awfully good pictures of these things nowadays with a barium enema', and I realized that he was not going to operate until the diagnosis had been thus confirmed. Apart from what Sir Robert Hutchison would have called the 'insult to my clinical instinct', this meant delay, discomfort, and expense, and much as I admired that surgeon's technical skill, I would not employ him again.

THE COMMENTS OF PATIENTS

I sometimes wish that our consultant friends could hear the comments that our patients later make upon them.

'Well, now how did you get on?' said I, to a man on his return from Harley Street, 'Did he help you? Did you like him?' 'Oh, I liked him', he said, 'I liked him—but I think he ought to wear braces!'

'That fellow has sent me a most preposterous account', said another, who had come brilliantly through a very severe surgical ordeal. 'Oh', said I, innocently, 'How much is it?' 'Absolutely ridiculous', he exclaimed, 'he's sent me an account for 175 guineas! Well, either 150 *or* 200, but not 175!'

'I can't talk to Dr. So-and-So', said a widow. 'Why not?' said I, 'He's a very charming man'. 'Yes, I know', she said, 'but he asks all the questions, and although I give him all the answers, I don't get a chance to *talk* to him'.

This is very modern, isn't it? She seems to have stepped straight out of Balint's book 'The Doctor, his Patient, and The Illness', in which he says, over and over again, 'If the doctor asks questions in the manner of medical history-taking, he will always get answers—but hardly anything more'.

THE TRUTH OR THE WHOLE TRUTH?

The new theory of general medical practice put forward by Balint is well worth study. The idea is that the patient comes to his doctor with one, two or more ideas, proposals or suggestions for an illness, e.g. he may say, though he is not likely to be as brief as this, 'Doctor, I have a lump in my neck, a pain in my back, and I don't get on with my wife'. Now which of these complaints is finally selected as *The Illness* depends entirely upon what the doctor has been taught at his hospital, and what he is interested in now. We all find lumps in the thyroid interesting and pain in the back a bit of a bore; whether we shall allow the patient to tell us about his unhappy marriage will depend upon how much time we have to spare.

Mackenzie had strong views on this subject.

'When the patient and physician come first together', he says, 'it often happens that there is an unconscious struggle who is to be dominant. Many patients come full of their own ideas about their complaints, with theories as to the nature and cause of their sensations, and eager to impart their own opinions. Or they come with a bundle of notes which they insist upon reading. The first question put to them: "Of what do you complain?" will immediately give them an opening, and they will, if not checked, proceed to indulge in an elaborate history of their troubles. This must be quietly and firmly repressed. The story of their life must be reserved until the examination is finished, and their replies must be limited to the sense of the question asked. If this is done, in a few minutes all the essential facts will have been obtained, and if then they are asked: "Is there any other point you have not mentioned?" they will gaze helplessly, and, in a surprised tone, acknowledge that all the facts have been obtained in five minutes, which they thought would take half an hour to tell'.

And yet . . . And yet . . . that still small voice—'If you ask questions, you get answers—and hardly anything more'. Is it not extraordinary that, although Sir James Mackenzie knew well that love can bring a blush to a young girl's cheek, he never realized that fear can bring a tremor to a strong man's heart?

'Here lies a most beautiful lady,
Light of step and heart was she'—

and very intelligent as well. At her request, I took her to see a distinguished man, her choice not mine, who, when asked what his fee would be for the services to be rendered, evaded that question, even when it was repeated. When we got out into the fresh air, I asked her, non-committally, what she thought of him. She gave me her dazzling smile, and said: 'I thought he was the most absolute cad I've ever met'.

'But beauty vanishes, beauty passes,
However rare, rare it be'.

Poor thing! When I returned after the war, I found that she had had a subarachnoid hæmorrhage and had been long in a mental institution. She was considered to be actively suicidal, but gradually signs of intracranial pressure appeared and increased, and she became more and more helpless. 'An aneurysm of the left internal carotid with 3rd nerve palsy, proptosis, commencing hemiplegia of the opposite side and the peculiar fatuity and outspokenness—the failure of control and the want of

inhibition—which is characteristic of pressure on the frontal lobe'—thus spoke the neurologist when she came home. An arteriogram was done, an incredible performance; apart from the anæsthetist, four technical assistants were required and the radiologist made use of them all.

A surgeon was invited to see her and, though clearly disinclined to advise operation in so 'psychiatric' a subject, he changed his view after seeing her, and comparing her present appearance with an early portrait and some fairly recent photographs. He thought the aneurysms, though big, were not sufficient to cause the pressure necessary to bring on the recent hemiplegia. That must have been caused by a bleeding, producing a temporary cerebral tumour, and 'this is confirmed by the bladder incontinence. The common carotid ought to be tied. It is less risky than tying the internal carotid. I cannot tell', he said, 'how much recovery she will make; it can hardly be complete, but it may well be partial. I would do it when convenient, for further improvement without it is unlikely, and disaster may occur at any time'.

It was done and great improvement followed; she was calmer, less giggly, less fearful and the hemiplegia disappeared. Soon, however, she began to fall, to vomit, to be incontinent. The physician gave his final assessment. 'The aneurysm is growing and gradually destroying the frontal lobe with increasing degradation of personality, as witnessed by increasing incontinence. The last phase of the illness is approaching and cannot be long delayed. She will either have another hæmorrhage or pass into coma, and there is absolutely nothing to be done'.

I have given these opinions at length because they are models of what such things should be—carefully considered, simply phrased, the truth as far as it could be known.

I have said that the family doctor receives, but does not necessarily adopt, the advice given. He may feel convinced that a particular line should be taken, but be unable at first to find anyone to agree with him. He must then bide his time, advocating his plan, here a little, there a little.

WHEN EXPERTS DIFFER

The family doctor really comes into his own when specialist opinions differ. In this dilemma, all look to him to find the right solution, and he must take his courage in both hands and rise to the occasion. Heaven knows, he will not always be right, but he will by this time have specialized on that particular patient to such an extent, and have thought so deeply about him, that he may fairly claim that his advice should be followed. In brief, he must get his own way; and if anyone thinks this is an overstatement, let me remind him of Iphicrates, the Athenian general, who was challenged in the Assembly to say who *he* was, to be so presumptuous. 'Are you an archer, a targeteer, a cavalryman, a hoplite?' 'No', said Iphicrates, 'I am none of these, but I command them all'.

An old friend, whom I had not seen as a patient for four years, came to see me on a Saturday afternoon. He complained of loss of weight, of precordial pain, of exhaustion, and of sweating at night. He lay upon my couch and I found in his abdomen a truly enormous spleen. I set to work on this, as I sometimes do in such a case, by showing him to a pathologist, who confidently promised an exact diagnosis from an examination of the blood. The blood count, however, proved most unhelpful—more than five million red cells, hæmoglobin 94 per cent., white cells in due proportion and without abnormality. I showed him to a physician, who was not convinced that it *was* a spleen, and feared a malignant growth. He suggested a barium swallow, an intravenous pyelogram, and a battery of chemical tests for

liver function; if these should prove negative, a surgeon. I decided to skip all that and we went to see the surgeon, who took me kindly by the elbow and said: 'I'm afraid this is a carcinoma of the stomach, probably too big for us to do anything with, and if we open him and do nothing, he may be dead in two months'. He asked for a barium meal, which seemed to show that the tumour had nothing to do with the stomach or colon, and it appeared therefore to be either a spleen or a retroperitoneal affair.

This is not a very uncommon situation—pathology blank, x-rays indecisive, specialists uncertain. What is to be done? The family doctor must accept the responsibility and make a decision, and to do that he should state the problem to himself in the simplest possible terms. Here that would be 'Can the patient hope to recover his health with this great mass of abnormal tissue inside him?' Obviously, not. 'Can it be destroyed by x-rays?' 'Perhaps, but then the diagnosis will never be established'. The decision therefore was for operation, at which a seven-pound spleen was removed.

MASTERLY INACTIVITY

An old lady, aged 79, fell and fractured her left femur. The fracture was pinned with a very good result indeed. A few years later she became my patient, and on ten separate occasions she fell, more or less heavily, but without serious injury. At last, within two weeks of her 89th birthday, she fell, so to speak, once too often, and fractured her right, her 'good', femur. By this time, she had a considerable degree of congestive heart failure and for two years had received mersalyl injections on an average once a fortnight. Her surgeon and I consulted together and summoned an anæsthetist. We asked him how he assessed her chance of surviving an anæsthetic, an operation, and the next twelve hours. He answered, '50-50'. It is a terrible thing that a patient should die after an operation, deliberately undertaken. The family doctor's conscience strikes him without mercy. We then stated the problem to ourselves in the simplest possible terms, 'Will she ever walk again?' Reply, 'No', for, reviewing her recent history, we could not possibly allow it. Therefore, nothing whatever was to be gained by operation. She recovered, she remembered not a thing of the four weeks she had spent in the nursing home; she lived another year and a half, and then died of old age.

CONCLUSION

A great deal of the art of consultation can be very simply stated: choose your man well, meet him yourself, remember that he is not infallible. A second opinion is a very poor substitute for a consultation. How much better to meet, to discuss, to agree, to explain to the patient and obtain his consent. It is now somewhat out of fashion to describe family doctors as the spearhead and/or backbone of the profession. Teamwork is the slogan and, if the family doctor is to be a member of the team, he must be the Brains of it and the Captain of it.

GENERAL PRACTITIONERS' FORUM

HOW IMPORTANT ARE PSYCHOGENIC SYMPTOMS?

By JOHN HORDER, B.M., M.R.C.P.

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THREE patients consulted me last week because of upper abdominal pain.

The first, a man of 55, had had slight pain for a month and had lost appetite. He had never had such symptoms before. A barium meal has since shown him to have a carcinoma of the stomach.

The second, a man of 24, had had acute pain for eight hours, with repeated vomiting and a little diarrhœa. He recovered completely within twenty-four hours. He had gastroenteritis.

The third, a woman of 35, had had indefinite discomfort intermittently for about three months, with normal appetite but increased passage of wind per rectum. There was also some disturbance of sleep. The symptoms were not typical of ulcer or other organic disease and it seemed fair to make a diagnosis of nervous dyspepsia.

There is no difficulty in deciding the relative importance of the first two cases. It was obvious that the second case, despite the severe pain, would recover rapidly, even without treatment. A day's rest and a single prescription would certainly suffice. The suspicion of serious trouble arose in the first case after five minutes of history-taking. It was clear that a barium meal had to be done urgently, and from the results of the barium meal it is now obvious that a laparotomy will have to be done very soon; it is also likely that the case will prove inoperable, that the patient will die after much suffering and that the doctor will have a prolonged and heavy task before him.

It is unlikely that any doctor will disagree about this estimate of the relative importance of these two cases. But how is the third case to be estimated? To this there is no easy or agreed answer. The purpose of this article is to look at two possible answers, to discuss which is right and to introduce some wider implications.

A CASE HISTORY

It would be reasonable to make a diagnosis of functional nervous dyspepsia in the third case without further investigation. Alternatively a barium meal might be done and it would prove to be normal. It would be reasonable to leave the matter at that and to cure the symptoms with a mixture containing a sedative, an alkali and an antispasmodic. This is undoubtedly the way in which many doctors would think it best to treat this patient. Such management assumes that the case is not very important: in fact, that it is in much the same category as the second case, the acute gastroenteritis. That the symptoms would probably make an immediate response to treatment would confirm this estimate. It is equally reasonable to wonder what causes the symptoms in this particular person. As it happens, I did inquire.

At first the patient was unable to explain, but after a while she became more at ease and it was not too long before she volunteered that there had been 'a bit of an upset' two months ago. There followed a story of which the following are the salient points:—She is married to a professional man of 38, but after eight years has no children. At the time when her symptoms started her mother-in-law was staying in her flat, recuperating from an illness which was in fact psychogenic. The mother-in-law, a widow, has been a nervous invalid for years and is closely attached to her only son, the patient's husband. The patient's husband is so tied to his mother that he telephones her daily, takes her (with his wife) on every holiday, and even travelled 10 miles to see her in the middle of one night 'for fear that she might have had an accident' (she had not). My patient is known to me as someone who does not complain easily.

The time-relation between the symptoms and the 'upset', which was in fact a major clash with the mother-in-law, was so close that cause and effect cannot be doubted.

In view of this story the case becomes more important. It is not just that it has now occupied three-quarters of an hour of the doctor's time. An unsatisfactory marriage has been revealed, with a husband who is excessively attached to his mother to the detriment of his wife; it is clear that the husband needs help though unlikely that he will seek it. There are factors here which have caused, and if unaltered will continue to cause, suffering to both husband and wife for years. Some of the fundamental elements of happiness are involved for them both. It is not unreasonable to suppose that their health is likely to depend on their happiness.

It is therefore possible to look on the third case as one which is important in much the same way as the case of carcinoma—deserving as much expenditure of medical time and effort. Such expenditure is unlikely to meet with success in the case of carcinoma; in the third case there does seem to be at least a chance of helping. The criterion of importance is, of course: 'How much does this illness affect the life, past, present and future, of the patient and her family?'. To answer this question, all relevant facts must be taken into account. It may be misleading to look only as far as the patient's body.

THE IMPORTANCE OF PSYCHOGENIC SYMPTOMS

This third case, like so many others which are presented to the family doctor, forces one to wonder how seriously one ought to take psychogenic symptoms in general. In this context I use the word 'psychogenic' in a wide sense to include such symptoms as anxiety, depression, insomnia, tremor; abnormalities of behaviour, such as excessive shyness or refusal to eat in children and sexual difficulties in adults; physical symptoms referable to various systems, such as palpitation, repeated need to take a deep breath, spots in front of the eyes, flatulence, certain menstrual irregularities.

This is an issue which faces the general practitioner more often than any other doctor, though it must also face the pædiatrician, the general physician and, one would hope, some medical administrators. The psychiatrist inevitably takes the symptoms seriously. The surgeon would usually be under pressure to pay little attention to such of them as come his way. But the family doctor who sees every type of case in succession has to weigh one

against another. He inevitably decides the issue for himself, whether consciously or unconsciously, and he acts daily according to what he has decided. In every case which he sees he automatically communicates to the patient whether he thinks the matter important or not, decides how much treatment should be given, encourages the patient to return or not, permits him to talk or discourages him.

It is traditional, at least in the last 50 years, to rate psychogenic symptoms rather low in the scale. The tradition is well-rooted in hospital teaching where, except in psychiatric departments, these symptoms tend to be labelled functional and the patients referred back to their own doctor. But there are signs that opinion is now changing about the correctness of this rating and the change may be reflected in teaching. For instance, in 'Recommendations as to the Medical Curriculum', published by the General Medical Council in 1957, it is written:—

> 'During his study of all clinical subjects the attention of the student should be continuously directed by his teachers to the importance of the interrelation of the physical, psychological and social aspects of disease'.

Our fathers were well aware that good health contributes to happiness, but perhaps we are more aware than they that happiness contributes to good health, and that it is therefore the doctor's concern. We are less inclined to deny the existence of atypical diseases and more willing to admit that emotions play a part in all illness. We are, in fact, tending to take psychogenic symptoms more seriously.

If one assumes that people cannot change and that all psychiatric guidance is useless, there is of course no point in taking psychogenic symptoms seriously. But the experience of those who make the attempt does not suggest that it is so hopeless. The example of my third case does show how important to the patient may be the issues which lie beneath trivial symptoms. To take a defeatist attitude is to risk missing the chance of helping someone in a serious crisis and in a matter which may influence deeply the rest of her life. There is another disadvantage in making light of these symptoms. If the doctor does so, it often happens that the patient comes back after an interval with the same or different symptoms. He is not cured and he is aware of this, although he does not know why. In this situation mythical minor diseases may have to be named to explain what is going on and to save the face of patient and doctor: 'dyspepsia', 'gastritis', 'colitis' or perhaps, as on the Continent, 'low blood pressure', 'the liver', 'the kidney'. In the suggestible patient this beginning can lead to a lifetime of invalidism, with consequences which are sometimes remarkable.

But all psychogenic symptoms are not so important. People vary greatly. It takes a severe strain to make some people anxious or depressed or liable to produce a small physical symptom. Others will do so after only small provocation. If one already knows the patient well it may be possible to decide whether or not a symptom is important without much delving, but

spot diagnosis in this field can be as misleading as in any other. As Sir Francis Fraser (1958) said recently:

> 'It is a good rule in clinical medicine never to be satisfied with what has been done for a patient until the evidence is sufficient for a prognosis to be given, even if it would be unwise to state it. The prognosis is the answer to the question, often unspoken, "What does this mean to me?" or "What does this mean to my child?" '.

Sufficient evidence, in a case with psychogenic symptoms, is seldom to be collected without cautious and kindly delving. When the evidence is collected it may sometimes be found that the underlying issue is trivial; but it is not a good rule to jump to this conclusion in advance. Nor should one fall into a common trap. A patient may have an atypical dyspepsia and live with a difficult mother-in-law. It does not necessarily follow that the mother-in-law is the cause of the dyspepsia. More evidence is needed.

SOME OBJECTIONS

A number of objections are still raised to the idea of taking psychogenic symptoms seriously:—

(i) 'There is not time'. This objection is important. Listening to and discussing these problems take a lot of time even if the doctor is skilled; it is unavoidable. It may well be that initial expenditure of time saves repeated later visits, but this is hard to prove. Under present National Health Service arrangements there is no satisfactory solution to this problem in general practice. Nevertheless, with changing concepts, the problem is going to arise more and more often and a solution will have to be worked out. This involves major issues.

(ii) 'To treat a psychogenic symptom makes it worse'. This is, of course, true for such hysterical phenomena as globus hystericus or a paralysis, if by 'taking them seriously' is meant treating them as if they were a physical disorder needing physical treatment. But to regard the patient with this sort of symptom as seriously disturbed emotionally is a prerequisite for helping him and does not aggravate the symptom at all. For other more common psychogenic disorders this objection does not even apply.

(iii) 'It is bad for neurotics to be taken seriously; it makes them think about themselves too much'. They think about themselves anyway because they cannot help it. It seems probable that suppressive treatment, directed at making the patient stop thinking about his troubles, may succeed in making him socially more acceptable for a time, but it does not cure. It is certain that no permanent increase in self-absorption results from taking these patients seriously.

(iv) 'It is bad for the public morale to take neurotics seriously; neurosis can become epidemic'. This potent but unreasonable idea is mixed up with another idea—that psychogenic illness is a moral weakness, not occurring in stoical people or in men of action. There is in fact no basis for the idea that to take neurosis seriously makes it spread. Nor is psychogenic illness incompatible with discipline, action, achievement, or indeed a contribution

to national life of the highest order; one has only to look at the lives of Isaac Newton, Florence Nightingale, Charles Darwin and Benjamin Disraeli.

Two hundred years ago the 'insane' were treated as criminals. For instance, in 1800 one patient at Bethlem was kept for nine years with iron collars round his neck and wrists and fettered to the wall with heavy chains. Fifty years ago, things were far better for the 'insane', but 'neurasthenics, neurotics and psychopaths' were still looked down upon as people with a moral failing, neither understandable nor curable. Things are better today for them, too. The acceptance of them as people with an illness is a prerequisite for their improvement. But maybe we still do not always listen to their troubles and give some of them the importance they deserve. Nor does this concern only those whom a psychiatric label segregates as abnormal. There are few of us who, during the course of some physical illness, or under some other unusual stress, show no trace of anxiety or its bodily accompaniments. We still tend to think that all such crises should be managed as if we were infantrymen about to 'go over the top', pretending that nothing is the matter. Such stoicism is to be admired but it sometimes leads to greater harm because unconfessed anxiety can remain unresolved. There are occasions when stoicism must be advised by the doctor, but they arise when cure is impossible. When cure is possible, this virtue can become an active hindrance.

SUMMARY

Every doctor instinctively decides for himself how important he considers psychogenic symptoms, compared with those of primary physical disease. His decision is displayed by the way in which he manages his cases.

There is wide variation in this assessment between doctor and doctor.

The present tendency is towards taking psychogenic symptoms more seriously. Reasons are given for believing this to be the right policy. Possible objections to the policy are considered.

I am grateful to Dr. Annis Gillie, Dr. Desmond O'Neill, Dr. Henry Wilson and my wife for helpful criticism.

Reference

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SOME OBSERVATIONS ON HOME CONFINEMENTS

By H. M. S. NOBLE, M.B., Ch.B.
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This is a semi-industrial practice. There are three large housing schemes within it and in each of these is a local authority 'Health Clinic', in which antenatal clinics are held for patients booked for home confinement.

Because these housing schemes are all fairly new—two of them are entirely post-war— they contain a large number of young married couples and the birth rate has been relatively high. This report is based upon a study of 100 consecutive patients booked for home confinement by me between April 1954 and April 1958.

SELECTION OF PATIENTS

As a general rule, patients were referred for hospital confinement for the following reasons:—

(1) If the mother herself requested to go to hospital.

(2) If there was a history of heart disease, hypertension, pulmonary tuberculosis, or diabetes mellitus.

(3) Cases of previous pre-eclampsia, ante- or post-partum hæmorrhage, repeated miscarriages and women over 38 to 40 years were referred to hospital. This latter group, however, if they had had several previous successful home deliveries, often refused to go to hospital.

(4) Patients who had had five or more confinements. One of the abnormal 'para 9' pregnancies (complete spina bifida) and the 'para 10' pregnancy (premature anencephalic fœtus and post-partum hæmorrhage) were one and the same patient who refused to go to hospital. She agreed to be sterilized after the second disaster, much to the relief of all concerned with her care.

(5) Social reasons: e.g. poor home conditions, unmarried mothers.

CARE DURING PREGNANCY AND CONFINEMENT

All patients were seen at one of the clinics monthly until 32 weeks, fortnightly until 36 weeks and thence weekly, or more often if thought necessary, until term. On all occasions the district midwife who was delivering the case was present. The routine examination was carried out by us both and the urines were tested by the midwife. I took blood for grouping during one of the early visits and did some hæmoglobin estimations at 32 weeks although this was not done routinely. Failures to attend were few and they were visited by the midwife or myself and usually attended satisfactorily thereafter.

The midwife was always present at the confinement and she delivered the majority herself. I attempted to see all the mothers at least once during the first stage, together with the midwife. I delivered some myself—especially during the first half of the series—and was present while the midwife delivered on many occasions. I was sent for by the midwife for any case in which she was in doubt and I was in attendance for all abnormal cases. One of my partners was present at both forceps cases and one of us gave the anæsthetic. The only case at which neither of us was present was the 'precipitate labour'.

About 10 per cent. of the deliveries were carried out at the local 'G.P.'

maternity hospital. These women attended at one of the three antenatal clinics and went to the hospital by ambulance when their labour started. No abnormal obstetrics was carried out and the conditions were the same as for home confinements except that the patient was under the care of the resident midwife in the hospital for her actual delivery.

RESULTS

The results are shown in table I. No mothers were lost.

Of the 19 primigravid cases, 14 had home deliveries with live babies. These included one case of retained placenta removed by the 'flying squad' obstetric team, and one case of forceps for second-stage inertia. One breech presentation was transferred to hospital during labour and had a live baby

Pregnancy	Number booked	Normal pregnancies and confinements	Abnormal pregnancies and confinements
Primigravida	19	12	6
Para 1-5	74	62	12
Para 7	1	—	1
Para 8	1	1	—
Para 9	3	1	2
Para 10	1	—	1
Para 11	1	1	—

TABLE I.—Analysis of 100 consecutive patients booked for home confinements.

delivered there. There was an anencephalic fœtus born at home which died, after five minutes. One patient was transferred to hospital because of delay in the first stage, and had a still-born hydrocephalic fœtus there. One patient had a miscarriage at twenty-four weeks and one moved to another district during her pregnancy.

Of the 81 multiparous cases, 68 had live babies at home. These included one set of twins, one 'face to pubis' forceps delivery and one case of retained placenta removed by the 'flying squad'. Three were transferred to hospital during pregnancy because of (a) gonococcal infection of the mother, (b) increasing degree of pre-eclampsia, (c) bronchial asthma. All had live babies in hospital. Three patients were transferred to hospital during labour: (i) one had a still-born anencephalic fœtus; (ii) one had a premature labour at 32 weeks, and the baby died; (iii) one had twins which were not diagnosed until labour began, both twins died later of atelectasis.

One mother had a precipitate labour; the baby was sent to hospital but died later as a result of cerebral injury. There were a still-born anencephalic fœtus and a still-born hydrocephalic fœtus. In the latter case there was a post-partum hæmorrhage controlled by intravenous ergometrine. There were four miscarriages.

CONCLUSIONS

It has often been said that all confinements should be carried out in hospital; possibly from the purely obstetric point of view this would be an ideal arrangement. In this area, however, it will be some considerable time before there are sufficient obstetric beds available for this ideal state to be attained. Further, there are certain drawbacks to hospital midwifery which patients have mentioned to me: e.g. they are often examined by several different doctors and nurses during their antenatal period and are somewhat worried as to who will be at their confinement; they have quite long periods to wait at the busy outpatient clinics; they only see their babies at feeding times in hospital and often come home without having had the opportunity to bath them. These are small points to the busy obstetrician with a large clinic, but they cause a good deal of anxiety to the expectant mother, especially if she is a young primigravida.

Provided that cases are carefully selected, it would seem that there is still a place for domiciliary midwifery. I have been very fortunate in this area in being able to work in close liaison with the district midwife. Together we have seen the mother from time to time during her pregnancy and have endeavoured to discover any developing abnormality early so that the patient may be referred for a specialist opinion if necessary and possible hospital confinement. My experience has not confirmed the view that the doctor must be present for every delivery. If the antenatal care has been satisfactory, I have found that the mother herself usually likes to be delivered by nurse. She has great faith in her nurse and knows that the doctor is immediately available if his help is required.

I have been fortunate also in being in a practice near several very helpful and efficient hospitals. A few of the patients in this series were seen willingly by them for obstetric opinions. The 'flying squad' came at once and dealt with my two cases of retained placenta. A number of cases, not in this series and booked for hospital confinement, were, with the approval of their hospital, looked after by our antenatal clinic to the 34th week for domestic reasons or because of travelling difficulties.

During this series I have had relatively few abnormalities to deal with: e.g. two cases of forceps and eight or ten perineal tears to repair. I had only one post-partum hæmorrhage which was controlled by intravenous ergometrine.

SUMMARY

One hundred cases of home confinement are described and discussed.

Careful selection of patients and continual antenatal care are of paramount importance in domiciliary midwifery. Because of this selection, experience in abnormal obstetrics is naturally slight.

The importance of the doctor and the midwife working as a team is stressed.

Good liaison with the local maternity hospital is to the advantage of the patient and all those who are concerned with her care.

DIAGNOSTIC INSTRUMENTS

A Method of Illumination

By A. M. W. PORTER, M.B., B.S., D.R.C.O.G.
Ship's Surgeon

It is perhaps not generally appreciated that diagnostic instruments, such as a proctoscope and vaginal speculum, may be illuminated from the battery and handle of an ordinary diagnostic set. I am told that at one time such a system was quite popular, but is now out of favour, possibly because most hospitals use the mains and a transformer as a source of power.

The following system utilizes a Keeler diagnostic set, but the principle is applicable to any make. A length of flex is led from a screw-in plug

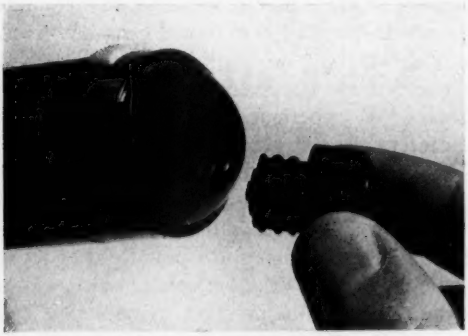

Fig. 1.—The battery handle and screw-in plug.

(fig. 1) to the female component of a flex plug, the male components being attached to the various short leads from each diagnostic instrument. This arrangement keeps the total length of flex down to a minimum. The 3-volt battery has proved sufficiently powerful to light instruments such as a proctoscope, sigmoidoscope, vaginal speculum, cystoscope, or a headlamp.

The advantages of this system are:—

(1) It is independent of mains electricity.

(2) The initial expense of a transformer is avoided.

(3) The 'power unit' is compact and lies readily to hand.

I have used this system for two years now and I can recommend it as being simple and reliable.

SECTION OF GENERAL PRACTICE OF THE
ROYAL SOCIETY OF MEDICINE

DISCUSSION ON COLONIC DISORDERS

November 19, 1958

Dr. K. H. G. Milne (*London, W.*1).—The diseases of the colon seen by the general practitioner can be grouped on the basis of their management. Some are mere incidents in the life of the patient and, after treatment, they can be forgotten. The major conditions, diverticulitis, ulcerative colitis, and malignant disease, represent an ever-present source of trouble. A third group, a hotch-potch of illnesses, can cause trouble on and off for years, but should interfere with the patient as little as their doctor can manage: the most notable of these is spastic colon. Undergraduate teaching must emphasize the need for full investigation of suspected malignant disease, and cases of diverticulitis and ulcerative colitis must receive it also, so that long-term management can be planned. But a complete diagnostic work-out, if given to a patient suffering merely from a spastic colon, will not only be a complete waste of effort, but will do positive harm; it will focus attention on symptoms, whereas the chief hope in treatment of these patients is in getting them to learn to live with their condition understandingly. Such investigations may sow the first seeds of fear of malignant disease, which will be the more difficult to eradicate at a later stage.

A general practitioner is likely to see one fresh case of carcinoma of the colon in a year, but he will see one new patient every week whose symptoms *could* be due to a large bowel growth. The numbers involved, quite apart from these other considerations, make the investigation of every suspicious case impossible at the start. There must be selection, based not only upon the history and the examination, but also on the early response to treatment. Our previous knowledge as a patient's general practitioner may be a help or may be a handicap, and each case is an individual one. Physical examination is most important.

There will be some patients who must obviously be investigated further; a few will stand out clearly as needing only reassurance, advice and antispasmodics. But the middle three-fifths are the worrying ones. It is justifiable to treat them for four to six weeks for the innocent condition they may very well have, and then to review them fully, rather than to keep them hanging about in uncertainty and without treatment while hospital appointments are arranged. Many of them have come more for reassurance than for relief of symptoms, and most of them will be entitled to reassurance anyway.

Management along these lines will clear one's own mind about the patient's condition; in those cases in which investigation is needed, the patient can then be encouraged to have the question pursued as far as is necessary. Once investigations are started, a negative barium enema by itself is not enough, and when this is the case the doctor ought to press for contrast air studies, or laparotomy, confident that investigations are not being done unnecessarily. Treatment given on a basis of spastic colon may relieve symptoms arising from a growth for a time, but this is not dangerous when the general practitioner remains in touch with his patient, and can recognize early that things are not going as they should. It is wrong to refer a patient to a consultant for a decision as to whether he should have investigations done, since he is without the general practitioner's special knowledge of the patient, and also because he is denied an opportunity to review the case. Once a patient is referred for a second opinion, full investigation cannot be avoided.

General practitioners are faced with a double duty: patients with malignant disease must come for treatment as early as possible, but patients with functional disorders must be protected from the full range of investigations. A reduction in the actual number of patients referred for investigation will help, in a positive way, those with functional conditions, and will make easier the complete investigation of the patients who need it.

Sir Ralph Marnham (*St. George's Hospital*).—The patient's symptoms are almost entirely a combination of alteration in bowel habit, the passage of blood or mucus, and some degree of abdominal pain. Careful abdominal and rectal examination will give much information but, if entirely negative, some patients can be treated for two or three weeks without going further. Obviously those with bad family histories will require thorough investigation at once. When these patients are referred to hospital, sigmoidoscopy should always be done as part of the routine examination. In the vast majority of cases the patient requires no preparation and certainly no anæsthetic. It is worth while for the stools to be examined for occult blood at an early date. Whilst constipation and/or diarrhœa may well be caused by a spastic colon, blood and mucus are nearly always produced by organic disease, the commonest in this country being ulcerative colitis, diverticulitis, and carcinoma.

Ulcerative colitis requires surgery if it is of the acute fulminating type which has failed to respond to a short course of cortisone, when the disease persists in spite of prolonged treatment—after eight or ten years, there is a real risk of carcinoma, and for various complications such as hæmorrhage, fistula, stricture, pyoderma and arthritis. Today the operation of choice is colectomy and anastomosis of the ileum to a short rectal stump.

Diverticulitis may produce symptoms of abdominal discomfort and bowel irregularity and a barium enema will show the presence of this condition. The severity of symptoms bears little relationship to the number of diverti-

cula present. The patient may complain of severe colicky pain, and on examination a mass may be felt in the left iliac fossa. Rest in bed, fluids only by mouth, the avoidance of aperients and an antibiotic such as tetracycline will usually cause the disappearance of the mass in four or five days. A subsequent barium enema is essential to exclude carcinoma. Some patients first present with an acute or chronic intestinal obstruction and a few with a vesico-colic fistula. These obviously require treatment by surgery.

Carcinoma.—Whilst in most of the other conditions the need for urgency when it exists is quite obvious, in carcinoma of the colon the urgency is there but the symptoms and signs may well be minimal and this is the worrying feature in the management of these cases. Patients may be afflicted at almost any age and obviously the earlier a diagnosis is made the better. The fact remains, however, that every patient must be judged on his merit. All I would add is to say that in addition to there being no undue delay it should be remembered that investigations may well have to be repeated if symptoms persist and a close contact maintained between all the doctors associated in looking after these patients.

Dr. J. F. Stokes (*University College Hospital*).—In a general medical clinic, with a gastroenterological bias, the colonic disorders we most commonly see are those due to functional change and those associated with diverticulitis and with ulcerative colitis. I propose to discuss four points which I have found of interest in this field: (1) the relationship of diverticulitis to pelvic abscess; (2) the difficulties provided by prolonged treatment of ulcerative colitis by corticosteroids; (3) the diagnosis of ileo-colitis; and (4) the management of functional colonic disease.

DIVERTICULITIS

In an ageing population we must expect to find more illness as a result of degenerative diseases, among which diverticulosis may reasonably be classed. When inflammation occurs in a diverticulum in the sigmoid colon (the commonest site of diverticula) it is not usually difficult to reach a diagnosis on the basis of left lower quadrant tenderness and rigidity, fever and leucocytosis. Difficulties arise in the more spirited section of the population, who regard constipation as their birthright, and attribute their abdominal pain to the doubtful habits of a cook, the Government, or the vagaries of the Meteorological Office. As the inflammation advances in this group it is more common, in my experience, for them to develop a pericolic abscess than a frank perforation; often this occurs in the Tom Tiddler's ground of the rectosigmoid junction and may escape notice until it achieves a considerable size, or points and partially discharges itself, sometimes per rectum but perhaps more commonly per vaginam.

If a barium enema fills the abscess cavity with radio-opaque material, the origin of the abscess is fairly clear, but often the abscess is walled off

and radiography simply demonstrates the presence of diverticula. It is in these circumstances that we find ourselves at a disadvantage.

Carcinoma of the colon may, of course, present with a pelvic abscess and the correct diagnosis is sometimes obscured by the biopsy report. It is important to remember that the histologist is not always the ultimate arbiter of the nature of disease.

Take for instance Mrs. L.S. She presented with a large pelvic mass and constipation in 1956; biopsy material taken from the mucosal surface of the stricture showed 'colloid carcinoma'. Two-and-a-half years later the steady advance of her cerebral arteriosclerosis made it necessary for her to be looked after away from home and the difficulty of disposal could only be overcome when re-examination, both clinical and histological, had shown that she had probably never had a carcinoma at all.

It is important to remember that the histologist is as much liable to observer error as any of us.

My first point, then, is that large pelvic inflammatory masses, masquerading as cancers of one sort or another, may often be due to diverticulitis and we should be very cautious in prognosticating on these cases.

CORTICOSTEROID TREATMENT

Now that so many patients receive corticosteroids, it is likely that most of us have at one time or another had experience of some of the complications of their prolonged use. In ulcerative colitis they carry special risks. There is a danger of postoperative collapse when ileostomy is undertaken in a patient who has had a long preoperative course of corticosteroids. Operation on a patient receiving corticosteroids always increases the corticosteroid requirement, and the risk can be avoided by stimulating the patient's own adrenals by corticotrophin preoperatively and by giving extra hydrocortisone at the time of operation.

I want to call attention to another difficulty, exemplified by Mr. F., who became apparently obstructed while on corticosteroid treatment. The question arose as to why this abdominal distension had occurred. Perforation is well known to occur in such circumstances and the clinical picture is usually atypical. Distension due to ileus may be the first sign. If the stool volume is high there may be gross potassium loss and hypokalæmia may result in dangerous distension. Œdema of the colon due to worsening of the disease despite the suppressive action of corticosteroids may also produce this picture. A low potassium state may be fairly easily excluded, but the decision as to whether to increase the dose of corticosteroids on the assumption that there is an exacerbation of colitis present, or to withdraw the drug in the belief that perforation has occurred, may be a matter of inspired guesswork. Obstruction, whatever the cause, must be overcome as expeditiously as possible, since the gut is friable and liable to perforate when distended for any reason.

In this case we tailed off the dose under antibiotic cover and were lucky in that he made a good recovery and returned to full work: his obstruction was presumably due to mucosal œdema.

ILEO-COLITIS

Ileo-colitis is a rare disease but, like many rare diseases, is not difficult to diagnose if its possibility is kept in mind. Diarrhœa has been stressed as a presenting symptom in most reported cases; in these circumstances both small and large bowels are naturally investigated.

In neither of two cases (both young women) whom I have seen recently was diarrhœa a leading complaint and it was this absence of frequent bowel motions which delayed diagnosis. In both cases it must be assumed that sufficient colon remained intact to carry out its normal drying and storing functions. The illness of the first patient had been considered to have a psychogenic basis. The signpost to the necessity for deeper physical examination was provided by a raised erythrocyte sedimentation rate (E.S.R.). The E.S.R. is a difficult investigation to assess and a rise in older people may be of little significance, but in young persons who are neither menstruating nor pregnant and who are not obviously the seat of focal infection, any abnormality should always be pursued. The diagnosis in the second case was delayed by the fixation of an exotic eponymous label which many sensible doctors had not felt able to challenge. She also had a raised E.S.R. and was subject to recurrent intestinal bleeding which had been attributed to corticosteroid treatment of her 'Behçet's syndrome'.

'SPASTIC COLON'

This syndrome comprises constipation, excessive mucus in the stools, spasm and pain in the colon muscle (often confined to the sigmoid) and pain and tenderness over a consequentially distended cæcum. By the time the patient seeks medical advice, a habit of over-purgation has, as a rule, been established. This state of affairs is unfortunately common and, although it usually stems from anxiety, its treatment on most occasions must lie in the hands of general physicians without resort to formal psychiatric assistance.

The first step in treatment must be to reassure both the patient and oneself that there is no organic obstruction in the colon, to clear the recto-sigmoid junction whose anatomy may escape the attentions of the most enthusiastic rectal finger, even at the expense of the irradiation which a barium enema inevitably implies. The colonic distension which both the preliminaries and the actualities of a barium enema provide may in fact produce temporary improvement in symptoms. Once this is done we have to assess, as we do in any psychosomatic disease, the relative importance of environmental circumstances and personality defect in its production, while using spasmolytic drugs and benign aperients in an attempt to achieve peripheral symptomatic control. Moral support and tolerance are quite as important as propantheline and belladonna in these circumstances. In some older patients, those in whom psychological depression lies behind their constipation and pain, electroconvulsive treatment may be worth consideration.

CURRENT THERAPEUTICS

CXXXIII.—ORAL HYPOGLYCÆMIC COMPOUNDS

By R. E. TUNBRIDGE, O.B.E., M.D., F.R.C.P.
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General interest in the possibilities of the oral hypoglycæmic compounds was aroused following publications of German workers (Achelis and Hardebeck; Bertram *et al.*) in 1955, although Loubatières and his colleagues had demonstrated the hypoglycæmic properties of certain sulphonamide derivatives as early as 1942.

CHEMISTRY

Two main groups of substances have been investigated, the 'guanidine' and the 'sulphonyl' derivatives. Several guanidine compounds, phenethyldiguanide (B.E.D.G.), amyl and isoamyl diguanide and decamethyl diguanide have been used in the clinical treatment of hyperglycæmia. This group of drugs produces hypoglycæmia by (*a*) increasing anaerobic glycolysis, (*b*) decreasing glyconeogenesis. These compounds are allied to 'synthalin', and in the past liver damage has been attributed to the use of 'synthalin'. Toxic reactions have been observed in a high proportion of the cases treated with these preparations, i.e. at least over one-third. These have been mainly gastro-intestinal. The therapeutic dose is very close to the toxic dose and any increase of dosage beyond 100 mg. daily is said to lead to the development of toxic manifestations. This group of preparations is of undoubted theoretical interest. So far, no reliable preparation free from a serious liability to produce toxic reactions is available.

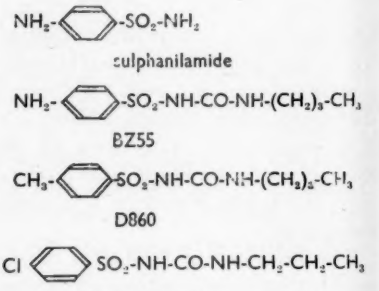

Fig. 1.—Chemical formulæ of sulphanilamide, BZ_{55}, D860 and chlorpropamide.

The sulphonyl derivatives and particularly the sulphonylurea preparations have provided the most interesting compounds to date, e.g. carbutamide (BZ_{55}), tolbutamide ('orinase'; D 860), and chlorpropamide ('diabinase'). Figure 1 shows the relationships of these compounds to sulphanilamide and to one another.

MODE OF ACTION

The precise action of the sulphonylurea compounds is still not known.

There is unequivocal evidence that the presence of the pancreas is essential for their action. It is thought that they stimulate the secretion of insulin by the beta cells of the islets of Langerhans, since following their administration the granules disappear from the beta cells. Experimentally it has been found impossible to procure a hypoglycæmic reaction in the absence of insulin. It is possible that any effect they may have on the liver is mediated through the insulin released by stimulation of the beta cells. It must be clearly understood that the sulphonylurea compounds are not a substitute for insulin even though they have a hypoglycæmic action.

Carbutamide and chlorpropamide are not rapidly excreted and remain in the body for considerably more than twenty-four hours after a normal therapeutic dosage. The cumulative action is not serious but it may take, in the case of carbutamide three to four days, and in the case of chlorpropamide five to six days before the full effect of the cumulative action has been attained. Tolbutamide, on the other hand, is rapidly excreted, the maximum action occurring within four to six hours after administration and the drug is usually completely excreted within ten hours. Tolbutamide should therefore be prescribed twice or three times daily.

THERAPEUTIC INDICATIONS

Carbutamide and tolbutamide are generally available and may be prescribed on form E.C.10. Chlorpropamide is still only available in this country from the manufacturers and is limited as yet to use for hospital patients.

Dunlop (1957) has suggested that the indications for the use of sulphonylurea compounds are: (1) development of the disorder after the age of 40; (2) no previous tendency to develop ketosis easily; (3) daily insulin requirements not exceeding 40 units, and (4) fasting blood sugar when receiving no insulin not exceeding 300 mg. per 100 ml. A history of repeated ketosis, the rapid development of ketosis on the cessation of the use of insulin, or during an infection, are generally agreed to be contraindications to the use of the sulphonylurea preparations. If a patient is on insulin and it is desired to try the oral preparations, it is usually wise to begin giving the sulphonylurea compound before the insulin is stopped and preferably to reduce the dose of insulin by from 10 to 20 units a day. Several attempts have been made to use tolbutamide or carbutamide to replace or supplement the action of insulin in patients requiring more than 40 units of insulin a day, and also in certain brittle or unstable diabetics in an attempt to reduce the swing of the diurnal blood sugar levels but so far there have been very few lasting successes with this combined form of treatment. It does seem essential to restrict the trial of the preparations to those patients without a history of ketosis and who have not had more than at the most 40 units of insulin a day. Another important contraindication according to some workers is obesity. Obesity in diabetics demands that they be put on a reducing diet and since gain in weight is one of the problems arising from

prolonged treatment with the oral hypoglycæmic compounds, obese patients are not so likely to benefit from their use.

Approximately half the known diabetic patients can be controlled by diet alone. Of the remainder, some 20-30 per cent. can be controlled by a small dose of insulin: that is to say, under 40 units of insulin a day. Theoretically, therefore, some 25 per cent. of known diabetics could be considered suitable for a trial with the oral hypoglycæmic agents. Unfortunately, from this percentage must be deducted those liable to ketosis, and those excessively overweight. As 80 per cent. of diabetics beginning with diabetes after the age of 40 are overweight, this means that one is left at the most with some 10 per cent. of diabetics in whom the use of the oral hypoglycæmic compounds is a likely practical procedure. Many tests have been tried in an attempt to decide whether a patient is likely to respond satisfactorily. Increasing experience has shown that so far no reliable quick test has been devised which can, with certainty, indicate the patient who is sure to respond. Some patients apparently do not respond for several days, even for as long as two or three weeks, thereafter the result is satisfactory. It has been suggested that some unobserved infection is responsible for this failure to respond but in most cases the presence of such an infection has never been proved. In the early days of the use of these preparations some workers brought all their patients into hospital prior to instituting therapy, in order to ensure that their diet was being followed and that a true assessment of the effect of the drugs could be made. It is certainly important to realize that when a patient is brought up frequently to an outpatient department, even if he is only given placebo treatment, there is likely to be considerable improvement in his condition because of the heightened interest taken in his welfare. Despite these criticisms most doctors now rely on treating the patients as outpatients using as an initial screening the indications already quoted.

TOXICITY

Carbutamide, as shown in fig. 1, is closely related to sulphanilamide and has similar effects on the bone marrow: leucopenia and agranulocytosis have been recorded following its use. Skin reactions, nausea, vomiting and jaundice have also been recorded. Root (1958), in reviewing the toxic reactions in 10,000 cases treated with carbutamide, reported a 5 per cent. incidence of toxic reaction, some of which proved fatal. For these reasons Duncan *et al.* (1956) found it necessary to issue a warning against the use of carbutamide. Marble and Camerini-Davalos (1957) found that an increasing proportion of patients treated with carbutamide developed abnormal bromsulphthalein and alkaline phosphatase values with increasing duration of therapy. Thus, long-term treatment with carbutamide, even in low dosage, may lead to the development of liver damage.

Chlorpropamide is very liable to give rise to nausea, vomiting and intes-

tinal symptoms and these symptoms almost invariably occur if the dose prescribed exceeds 500 mg. daily. Jaundice, skin lesions and leucopenia have also been reported, although recent articles in the British press are conflicting in their evidence as to the incidence of toxic reaction. Murray *et al.* (1958) reported no serious toxic effects during the treatment of 43 patients. Walker (1958), on the other hand, in a similar number of patients, recorded the occurrence of nausea, vomiting and anorexia in fifteen and vertigo with lateral nystagmus in nine.

Tolbutamide is the least toxic of the three compounds. Nausea, vomiting and anorexia have been reported but so far no cases have been recorded of agranulocytosis. Headache may be associated with the administration of the drug and a cherry-red flushing of the face is liable to occur if strong tea or alcohol is taken shortly after the administration of the tablets. Marble and Camerini-Davalos (1957) found toxic reactions with tolbutamide in 0.9 per cent. of their cases, whereas with carbutamide the incidence was 9 per cent.

SELECTION OF PREPARATION

Tolbutamide.—The lowered incidence or mildness of the toxic reactions to tolbutamide has made it the preparation of choice. It is customary to prescribe an initial dose of 0.5 gramme twice daily to be taken before breakfast and tea. It is advisable to check the effects of treatment not merely by relying upon urine analysis but also with blood sugar estimations and regular monthly attendances. The dosage may be increased to 1 g. twice daily or even to 1 g. three times a day, but once 3 g. have been prescribed it is unlikely that further increase of dosage will be followed by any marked improvement in control if a high dose has to be continued for a long time. The value of tolbutamide was illustrated in a double blind trial by Hurwitz and McCuiston (1957). The control was a tablet of dicalcium phosphate and the analysis of the results was completed before the nature of the preparation used was known. Thirty-two patients were used in the trial and 26 reported that they were better with tolbutamide than with the placebo and none were better using the placebo alone. Some patients do not respond to tolbutamide initially and are referred to as having a primary resistance. Others develop this resistance later and are referred to as being cases of secondary resistance. It is not always easy to be certain whether the secondary resistance is really an acquired resistance to the drug, an exhaustion of the islet cells, or carelessness on the part of the patient due either to the false sense of well-being or to the neglect of scrupulous attention to the diet.

In a personal series of 97 patients treated with tolbutamide for more than a year, only 46 remained in reasonable control at the end of twelve months. The reasons for failure in the 51 were toxic reactions in two instances (one gastro-intestinal and one persistent headaches), the development of ketosis in association with infection in two, and in the remainder there was no obvious cause. In 13 cases secondary resistance developed during the first

three months of treatment but the remainder fell into no special grouping and occurred throughout the year. This experience is not unique, the percentage of success having varied with different observers from some 50 to nearly 80 per cent., and the figure has usually been lower the longer the trial has been continued.

Another development of continued treatment with tolbutamide is an associated gain in weight, which may be as much as some 12 to 26 lb. (5·5 to 12 kg.) during the course of a year. This increase in weight seems to be associated with the treatment and has occurred in patients who had adhered scrupulously to their diet. The excessive weight gain led to the stopping of tolbutamide therapy in six patients.

Carbutamide and *chlorpropamide* are much more powerful hypoglycæmic agents than tolbutamide but they are also more likely to cause toxic reactions. The dosage of carbutamide is 0.5 to 2 g. daily using it in one dose, and in my experience it is wise not to prescribe a higher dosage than 2 g. daily. Chlorpropamide has a much narrower range of dosage. It would seem that more than 500 mg. a day should not be prescribed and that a normal dosage is likely to vary from 100 to 500 mg. daily; 250 mg. is recommended as the initial dose.

CONCLUSIONS

(1) The oral hypoglycæmic compounds have a definite place in the treatment of the stable, non-obese, non-ketotic diabetic, who requires no more than 40 units of insulin a day.

(2) Approximately 10 per cent. of all diabetics may benefit from the use of oral hypoglycæmic agents but not all these will continue to respond if the treatment is prolonged over months or more than a year.

(3) Tolbutamide is the safest oral hypoglycæmic agent available today but secondary resistance to its action often develops during prolonged treatment.

(4) Carbutamide and chlorpropamide are more powerful hypoglycæmic agents than tolbutamide but great care must be exercised in their use as toxic reactions are both more frequent and more severe.

(5) It is still too early to say what place the oral hypoglycæmic agents have in the prolonged treatment of diabetes mellitus.

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PRACTICAL DIETETICS

I.—LOW-SALT DIETS

By ETHEL P. SKINNER, S.R.N.

Chief Dietitian, St. Thomas's Hospital

THE correct interpretation of 'low-salt diet' is 'low-sodium diet', for it is sodium which is restricted by careful choice of foods for this diet, whilst chloride at the present time is relatively unimportant. It is not possible to construct a 'salt-free' diet unless it is to consist only of water sweetened with glucose or sugar. A diet which specifies 'No added salt' can be useless as a therapeutic measure. This is usually taken to mean that salt may be used in cooking, but no further salt may be added to the food at the table. The choice of foods in this type of diet will often include those which have a high sodium content, whilst a considerable amount of sodium is absorbed by vegetables cooked in salted water.

A low-sodium diet is commonly used in conjunction with mercurial diuretics when œdema is present in the tissues. The relief and comfort which patients can obtain from this treatment are considerable provided they are encouraged to persevere, and are given guidance in the management of this diet.

The average daily intake of sodium chloride is 10 to 15 grammes in normal individuals according to the kinds of food eaten and the amount of salt added at the table. A low-sodium diet usually means restricting the sodium intake to 500 mg. (22 mEq.), or lower still to 200 mg. (9 mEq.).

CHOICE OF FOODS

To plan a low-sodium diet successfully it is very important to know which foods must be left severely alone, which can be taken in a limited quantity, and which can be taken freely because their sodium content is very low. Common salt has been added to food as a method of preserving for centuries, vegetables grown in the summer have been 'salted down' into crocks for storage, and adding salt to food at the table is a natural habit. It is necessary to understand that any food preserved with the addition of sodium chloride, or any food to which it is added during manufacture, cannot be included in this diet.

HIGH-SODIUM FOODSTUFFS

The following foods fall into this category:—

Cereals:	All makes of brown or white bread. All special breads unless known to be salt free. Self-raising flour. Baking powder. Cream crackers, digestive and water biscuits. Macvita, Ryvita, Vita Weat. All savoury and cocktail biscuits. All shop cakes, scones and sponges. Gingerbread. Breakfast cereals with added salt.
Cheese:	All manufactured cheeses, whether spread or hard variety.
Drinks:	Bournvita, cocoa powder, Horlicks, tinned tomato juice, beer.
Fats:	Salt butter and salt margarine. Bacon fat.
Fish:	Bloaters, kippers, smoked haddock. Shell fish—all kinds. Tinned fish—all varieties. Fish paste.
Flavourings:	Salt, mustard and vinegar pickles. Mayonnaise, salad cream and sauces. Bisto, Bovril, Marmite, Oxo.
Meat:	Bacon and ham. Sausages—fresh or tinned. Prepared meat, shop pies. Tinned meat or poultry. Meat paste. Pickled meat and tongue.
Soups:	All canned soups, e.g. cream soups, meat and vegetable soups. Packet and powder soups. Calves' foot jelly.
Vegetables:	Those cooked in salted water. Frozen vegetables if with added salt. Tinned vegetables (see under low-sodium products).
Miscellaneous:	Golden syrup. Rennett. Milk chocolate, cream toffees, liquorice. Sodium bicarbonate. Mincemeat. Salted nuts, olives, pea-nut butter.

LOW-SODIUM FOODSTUFFS

It is necessary to consider in detail the foods which can be included in a low-sodium diet. Many of the foodstuffs already mentioned are in daily use and not normally considered 'salt' to taste, but when sodium is removed from them the taste is entirely different, the result being a 'flat' product. It is therefore most important to pay particular attention to the replacement of flavour in the preparation of a low-sodium diet.

In order to avoid repetition in the suggestions which follow it must be remembered that salt and sodium bicarbonate are omitted from all cooking, including cakes, pastry, fish, meat and vegetables.

Cereals.—Cakes, pastry, scones and sponges should be made with plain flour and a special low-sodium baking powder. Suitable fats for use in cooking are lard, or unsalted margarine or a mixture of both. A little sugar or dried fruit adds flavour to scones or they can be eaten with jam. Pastry may be used to make jam tarts, fruit flans and tarts or meat pies. Icing sugar may be shaken dry on to cakes or made into water icing or butter

icing using unsalted butter or margarine and suitable flavourings, and used on large or small cakes.

Some difficulty may be experienced in finding a baker who is willing to make unsalted bread, but this is an essential, as ordinary bread eaten in any quantity will quickly double the daily sodium intake. Not many people have time to bake bread at home, but in some cases it may be a solution to the problem. Yeast and low-sodium baking powder can both be used for this purpose in conjunction with unsalted fats. Toasting unsalted bread or frying at breakfast time help to make it more palatable. 'Energen rolls' and 'Matzos' are suitable substitutes for unsalted bread.

Oatmeal and porridge oats (both made with water) can be used at breakfast time, as can shredded wheat and Energen breakfast flakes. Cereals at breakfast present a slight difficulty when milk is restricted to ½ pint (300 ml.) daily, but they can be eaten with fruit and added sugar.

Cornflour, custard powder, rice, semolina, spaghetti and similar cereals are all suitable but, if milk is restricted in quantity, it is not possible to make milk puddings or sauces. Rice and spaghetti boiled in water may be taken with meat dishes.

Cheese.—The only cheese available is unsalted cottage cheese which is similar to cheese made at home from sour milk. This is an insipid product when salt is omitted; chopped parsley or a very small amount of grated onion are possible but not popular flavourings.

Drinks.—Black tea or coffee, milk may be added from the daily allowance. All fruit squashes or canned fruit juices, tonic or soda water. Ovaltine—preferably restricted to one teaspoonful daily. Wines and spirits as allowed by the doctor.

Eggs may be cooked in any way, avoiding bacon fat for frying and salt butter or margarine for scrambling. Mushrooms, chopped parsley and tomatoes are suitable additions to an omelette.

Fats.—Suitable fats include unsalted butter which should only be bought in small quantities as its keeping properties are not very good. It is necessary to emphasize that 'unsalted' butter is required, 'fresh' butter can be interpreted as new delivery. Special unsalted and Kosher margarine are available from stores; both have a low sodium content. Cooking fat and lard can be obtained without difficulty and used in cooking as well as for frying or grilling, whilst dripping acquired at home will be useful either on bread or again for frying. Frying is an excellent way of adding flavour to many foods, but may not be suitable for all patients. Dairy cream has a low sodium and high calorie value, and finds its way into a number of homes.

Fish obtained from the sea has a comparatively high sodium content, but is usually allowed in moderation except when a very low sodium intake is required. White fish, e.g. cod, halibut, plaice or sole, may be fried or grilled with unsalted fats. Herrings may be grilled, or soused in the usual way avoiding the seasoning. Cod's roe and herring roes are permissible but not

always popular, whilst home-made fish cakes with chopped parsley make a change at breakfast or supper.

Fried fish obtained from a fried fish shop or eaten in a restaurant may have salt in the batter; if this is avoided there will be no additional intake of sodium. Pepper, lemon juice or vinegar are suitable extra flavourings. Fresh-water fish may be used freely but is not very popular without seasoning or sauces.

Fruit of all kinds. This includes all fresh fruit, cooked or raw, bottled or tinned fruit. Dried fruit if used in cakes or puddings should be restricted to a small quantity only. Prunes and figs should only be used occasionally.

Milk has a high natural sodium content; the daily intake should therefore be restricted to ½ pint (300 ml.) or less.

Vegetables.—Most vegetables cooked without salt have a low sodium content, and mint when available adds flavour to cooked vegetables. Carrots, celery and spinach, however, should be avoided if a very low sodium intake is required.

Potatoes after boiling may be mashed with unsalted margarine or they can be chipped or fried or roasted. Vegetables may be grated and eaten raw, salads may be flavoured with lemon, vinegar or a dressing of oil and vinegar. Dehydrated and dried vegetables such as butter beans, lentils and peas may be used in this diet provided they are not soaked in water containing salt or sodium bicarbonate.

Miscellaneous.—The following may be included provided they need not be restricted for any other reason:—

Glucose, sugar.
Barley sugar and barley sugar sweets. All boiled sweets.
Marshmallows and Turkish delight.
Honey, jam, jelly jams and marmalade.

MANAGEMENT AT HOME

It is a well-known fact that food cooked with salt has a much better flavour than food which has salt added after cooking. In some households it would be difficult to find sufficient saucepans or gas rings to cook salted and unsalted vegetables separately. The most economical way of overcoming this difficulty is to cook the vegetables for everybody without salt, remove the required unsalted portion just as they are cooked, and add salt to the remainder for a few minutes before straining and serving. This method can also apply to meat dishes, e.g. stews made in a saucepan or meat braised in the oven. Joints for roasting, if cooked without salt, are suitable for inclusion in this diet, whilst gravy can be made without salt, divided and flavoured as in the case of vegetables. All fresh meat is suitable for use in this diet including liver and kidney occasionally; and chicken or other poultry if available.

The management of cakes and pastry is not quite so easy, but the 'rubbing in' and 'creaming' can be done with unsalted fats; in the case of pastry the mixture is then divided before mixing with water and salt added to one

part. In the case of cakes, part of the unsalted mixture can be placed in a tin ready for cooking and salt added to the remainder. When a mixture is divided in this way to make unsalted and salted cakes some difference should be made between them, e.g. colour, plain or fruit, or they should be cooked in a different baking tin.

Chutney can be made at home with little trouble and improves cold meat and salad, or even some hot dishes. To make this use a recipe from any cookery book but omit the salt. The uses of mint sauce can be extended beyond that of roast lamb or mutton; it is quite useful to have a bottle prepared and available for any meal. Curry powder has quite a high sodium content, but can be used in small quantities occasionally to make a sauce for meat or fish. This dish provides a definite flavour which is often appreciated; if eaten with boiled rice the sodium content will be slightly lower than with potatoes. Bay leaves, cloves and thyme are all suitable for flavouring meat and fish dishes; sage and onion may be incorporated into forcemeat balls and stuffing using unsalted breadcrumbs.

LOW-SODIUM PRODUCTS

Dietade low-sodium canned peas (mint flavoured) and baked beans in tomato sauce are so far the only tinned vegetables suitable for inclusion in this diet. Their definite flavour makes them popular with patients, they can be used with both meat and fish.

Dietade low-sodium salad cream and tomato sauce are also available.

Edosol is a synthetic low-sodium milk powder. This should be reconstituted according to directions on the tin—preferably with a whisk; it is fairly expensive to buy. It is possible to cook with it, e.g. rice (preferably cooked in a double pan), or to use it for making custards (baked or boiled) and cornflour moulds. When reconstituted Edosol can also be used for drinks and flavoured with coffee or Ovaltine. It is invaluable in planning a high-protein low-sodium diet.

Energen—breakfast flakes and rolls.

Rakusens—Matzos, thin water crackers.

Ryvita crisp bread—without salt, obtainable direct from the factory and only available in 3-pound cartons.

Yeast extract (*unsalted*)—made by Marmite is useful for flavouring gravies, soups or meat dishes; this is only obtainable in 1-pound containers.

Salt substitutes.—These must be sodium free, Neo-Selarom and Ruthmol are potassium substitutes and are both suitable for use in this diet. They can be used in cooking, but should preferably be sprinkled on food just before eating.

Low-sodium baking powder.—Obtainable from any chemist if specially ordered.

Recipe:	Starch	28 grammes
	Potassium bicarbonate	40 grammes
	Tartaric acid	8 grammes
	Potassium bitartrate	56 grammes

Keep in a screw-top jar. Use slightly more than ordinary baking powder.

LOW-SODIUM DIETS

Karrell Diet

Calories 530. Protein 24 grammes approximately. Sodium 400 mg. (17 mEq.). The diet consists of milk, 800 ml., given in four equal feeds of 200 ml.

This is very restricted and quickly becomes monotonous for the patient. It is not often continued for longer than a few days.

200 ml. is approximately 7 fluid ounces or one glassful.

Diet I

Calories 800 approximately. Protein 30 grammes approximately. Sodium 230 mg. (10 mEq.).

Breakfast:
- Small portion fruit with sugar.
- 1 ounce unsalted bread, plain or as toast with unsalted butter or margarine.
- Marmalade or honey if desired.
- Tea to drink with milk from allowance.
- Sugar as desired.

Mid-morning:
- Fruit juice with some water, sugar if needed.

Dinner:
- Small portion of unsalted meat or fish or chicken.
- Small portion of mashed unsalted potato, *or*
- Unsalted bread with or without unsalted margarine.
- Small portion of vegetable cooked without salt.
- Jelly or portion of easily managed cooked fruit.

Tea:
- 1 ounce unsalted bread and butter *or* unsalted cake or scone.
- Tea to drink with milk from allowance.
- Sugar as desired.

Supper:
- Egg boiled or poached *or* unsalted soup.
- 1 ounce unsalted bread plain or as toast, with unsalted butter or margarine.

Bedtime:
- Small cup of warm milk.

Daily:
- Milk restricted to 7 fluid ounces. Glucose or sugar as desired.

Note:
- Small drinks of fruit juice with added sugar, or additional drinks of tea using milk from allowance may be taken, according to the total amount of fluid allowed daily.
- Many patients with œdema automatically restrict their fluid intake and, if necessary, they should be given guidance in this respect.
- The calorie value of this diet will depend to a great extent upon the amount of glucose or sugar used.

Diet II

Calories 1,600 approximately. Protein 65 grammes approximately. Sodium 400 mg. (17 mEq.).

Breakfast:
- Orange or grapefruit or other stewed fruit.
- Egg cooked in any way using unsalted fat.
- 1 ounce unsalted bread, plain or as toast, with unsalted butter or margarine.
- Honey, jam or marmalade as desired.
- Tea with milk from allowance, sugar as desired.

Mid-morning:
- Drink of tea or coffee using milk from allowance *or* fruit-juice drink.

Dinner and supper:
- Portion of meat hot or cold, or liver, or chicken or white fish, *or* egg cooked in any way without salt.
- Average portion of potato, chipped or roast or mashed with unsalted fat.
- Vegetables as available cooked without salt, *or*
- Salad with low-sodium salad cream or vinegar.
- Fruit fresh or tinned or stewed with sugar or fruit salad, *or*
- Pastry or sponge pudding made with plain flour, unsalted margarine and low-sodium baking powder.

Tea:
- 1 ounce unsalted bread, plain or as toast, with unsalted butter or margarine.
- Jam or other preserve as desired.
- Cake or scone made from plain flour, unsalted margarine and low-sodium baking powder.
- Tea to drink with milk from allowance, sugar as desired.

Bedtime:
- Drink as at mid-morning if required.

Daily milk allowance ½ pint (300 ml.).

LOW-POTASSIUM DIETS

Potassium is very widely distributed in animal and plant life, and it is therefore difficult to plan a diet with a low potassium intake which will be acceptable to a patient for any length of time. The average daily intake in normal individuals can be as high as 200 mEq., whilst it is not uncommon for many patients to have a daily intake of 60 to 100 mEq. These figures appear high, but the daily intake will naturally depend not only on appetite, but also on the kind of foods eaten. If there is a need for a low-potassium diet, then some restriction will be imposed not only on the choice of foods but also on the amount consumed.

Diet of Approximately 30 mEq. Potassium

Calories approximately 1,550.

Breakfast:
1 egg, boiled or poached.
1 slice bread, plain or as toast, with butter or margarine.
Marmalade if desired.
1 cup of tea with milk from allowance.
Sugar as desired.

Dinner:
Average portion of meat (boiled rice if desired).
1 slice bread, plain or as toast.
Average portion of cabbage or carrots.
Stewed apple.
Small portion of rice or other milk pudding (about 3 tablespoonfuls).

Tea:
1 slice bread with butter or margarine.
Jam if desired.
1 cup of tea with milk from allowance.

Supper:
1 slice bread, plain or as toast, with butter or margarine.
Small portion cheese or cold meat.
Small portion salad.

Bedtime:
Remainder of milk as a drink.

Daily:
Milk restricted to ½ pint. (300 ml.)
Sugar may be taken as desired. Salt may be used in cooking.
Fresh or bottled lemon should be used for drinks during the day with or without added sugar.
Tea and coffee should be limited because of their high potassium content.

To reduce the potassium content of any diet avoid:—

All dried fruit, particularly apricots, prunes, dates.

All nuts.

Potatoes, especially chipped and roasted.

Milk in excessive amounts.

Vegetables, tomatoes and other salad material in large amounts.

Fruit except stewed apple, tinned pears and pineapple, and lemon juice.

REVISION CORNER

SNEEZING

A SNEEZE is easily recognized to be a sudden involuntary audible expulsion of air through the mouth. It is a reflex phenomenon and seems to be without purpose. It is sometimes described as a protective reflex but to say that its object is to remove a causal irritant from the nose is unconvincing, for the blast of air comes out by the mouth. Also it can be initiated by a bright light which surely does not irritate the Schneiderian membrane.

PHYSIOLOGY

The afferent stimuli which result in a sneeze generally start in the anterior part of the nose and are referred by preganglionic fibres to the sphenopalatine ganglion. It is known that stimulation of this ganglion causes secretion of the nasal glands. As well as being affected by stimuli arising via the nasal branches of the trigeminal nerves this ganglion can also be influenced via the skin and the cerebrum. Post-ganglionic fibres from the sphenopalatine ganglion cause dilatation of nasal blood vessels and a discharge of a clear secretion. It is this secretion which stimulates the fibres of the trigeminal nerve. Impulses pass to the respiratory centre and fire off the efferent pathway which results in the sneeze. The nasal secretion also gives rise to the stimulation which causes the pleasurable feeling associated with sneezing.

Normally the muscles concerned with inspiration are coordinated by impulses coming to the respiratory centre by the vagus nerves from the lungs but in sneezing the impulses reach it from the nose and also from various parts of the body via the nose. In ordinary respiration expiration is a passive process depending upon the elastic recoil of the thorax but in sneezing it is reinforced by the muscular action of the diaphragm and abdominal muscles. The afferent impulses of the reflex cause first a large sudden inspiration and then a sudden forcible expiration. Just before expiration the palate is raised and the superior constrictor of the pharynx contracted so that the respiratory passages are shut off from the nose; then the contraction of the diaphragm and abdominal muscles causes the intrapulmonary pressure to rise. The nasopharynx is forced open and air is driven out. Involuntary closing of the eyes seems to be part of the reflex.

Sometimes a person may sneeze 'the wrong way' so that the main blast of air comes out of the nose. Apparently there is some incoordination of palatal movements and the result is a 'pharyngeal sneeze', a sort of unpleasant combination of a sob and hiccup. A sneeze can often be inhibited by pressing hard on the upper lip or occluding one nostril. When a stimulus is sufficient only to cause a desire to sneeze, a further stimulus such as looking at a bright light will often precipitate sneezing. An old-fashioned remedy for frequent sneezing was to place a camomile flower in each nostril. The noise of the sneeze originates in the mouth and not like that of the

cough in the larynx. It varies in different people and some can control it to a certain extent:–

A bugler named Douglas MacDougal
Found ingenious ways to be frugal
He learned how to sneeze in various keys
Thus saving the price of a bugle.

HISTORY

Sneezing has been a subject of discussion through the ages and there is much superstition about it. It is said that Prometheus introduced the sneeze to mortals. He made a statue which he wished to endow with life and to do this he stole a beam of sunlight. Wishing to conceal the theft from Apollo he hid the beam in his snuffbox. Shortly afterwards when taking a pinch of snuff he absentmindedly put the beam up his nose and this caused violent sneezing. Hippocrates considered sneezing dangerous in pulmonary affections but useful in other diseases. Aristotle pondered over the question as to why people treat sneezing as something holy and yet do not look upon other forms of release of air from the body as things worth worshipping. Perhaps it was because the head was regarded as a seat of genius. According to the Talmud it is a very favourable omen to sneeze during prayer because sneezing is a pleasure sent from God, and if God makes a man sneeze he will also answer his prayers.

The practice of saying 'God bless you' when anyone sneezes is very common in many countries. It probably originated at the time of Pope Gregory the Great (540 to 604) when plague was raging. Sneezing was a common feature and death generally occurred. The Pope therefore introduced a short benediction to be used when a patient's horrified friends heard him sneeze. They said 'God bless you' meaning no doubt 'God help you'. On the other hand, Jewish rabbis maintain that Adam sneezed for the first time at the exact moment when our first mother held the apple for him to take a bite. Adam regarded the sneeze as of evil omen and a presage of death. This was believed until the time of Jacob. When he sneezed he did not want to die and so besought the Deity to change the order of things. His prayer was granted and from that time it has been a custom for bystanders, when one sneezes, to wish him health and happiness. A single bout of sneezing in a tiny infant is regarded with pleasure and as a sign of good health and it is interesting to remember that when the prophet Elisha (II Kings, 4, 35) revived the dead son of the Shumanite with his prayers, the first sign of new life was shown by seven consecutive sneezes.

SNEEZING AS A SYMPTOM

Symptomatically a sneeze is usually of minor importance and only when it is persistent does it call for medical attention. Occasionally there is an obvious removable irritant such as long hairs impinging on the septum. Persistent sneezing is generally hysterical in nature. There are many recorded examples, such as that of a girl of 13 who sneezed continuously for two months and stopped when placed in a private room and prevented from seeing newspaper

men. There is good evidence that paroxysmal sneezing may sometimes replace the paroxysmal cough of pertussis. A complaint of frequent sneezing calls for a full examination of the ears, nose and throat. Conditions such as nasal polypi and even a foreign body in the external auditory meatus have been found to be responsible. Sinister effects have on rare occasions followed sneezing. A fracture of the thyroid cartilage has been reported and a bout of sneezing has greatly aggravated the symptoms of a prolapsed disc. Sir Jonathan Hutchinson regarded sneezing as a sign of health and said he did not recollect having seen any but fairly healthy persons sneeze. The idea that the sick don't sneeze, however, is quite untrue; they can and do sneeze and if they have pleurisy or lumbago the sneeze is very painful. Hippocrates said that a bout of sneezing might cure hiccup and so snuff may be given in an attempt to use sneezing as a therapeutic measure.

PUBLIC HEALTH ASPECTS

The all-important component of a sneeze is the highly atomized oral discharge. High-speed photography at 1/15,000th of a second shows that droplets of a size of 0.1 to 2 mm. are expelled at a speed of more than 100 feet (30 metres) per second. The number of droplets from the nose is insignificant compared with those from the mouth. Droplets are expelled from 1.5 to 5.5 feet (0.5 to 1.75 metres) and then fall. Sneezing is not an important factor in direct contamination of air, for most of the particles have settled within a minute. Only four per cent. have been found to be suspended for as long as forty minutes. Sneezing, however, contributes greatly to the secondary bacterial reservoirs in floor dust, handkerchieves, and the like. There is therefore justification for the slogan 'Coughs and sneezes spread diseases'. A large handkerchief carefully used prevents the scattering of droplets, but the polite use of the hand is much less efficient. After one sudden sneeze the handkerchief should be ready for the next one. Sneezing into an open fire is probably the most effective measure in preventing spread of infection by sneezing.

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THE PUPILS IN HEALTH AND DISEASE

The points to be considered in the examination of the pupils include their size, shape, regularity, equality, and reactions to light, accommodation and convergence.

PHYSIOLOGY

The size of the pupils is controlled by two mutually antagonistic, unstriped muscles: the sphincter or constrictor pupillæ, innervated by parasympathetic fibres through the third cranial nerve, and the dilator pupillæ, receiving its nerve supply from the cervical sympathetic. The constrictor fibres travel in the third nerve and terminate in the ciliary ganglion; from here the post-ganglionic fibres run forward as the short ciliary nerves to end in

the muscle. These constrictor fibres are activated reflexly by light falling on the retina. The pupillary reaction to light may be impaired by any lesion affecting the afferent side of the reflex arc, from the retina through the optic nerves, chiasma and tracts to the lateral geniculate bodies and the mid-brain. Lesions of the visual pathways above the lateral geniculate bodies, that is, in the optic radiation or visual cortex, do not interfere with the light reflex. Light entering one eye causes pupillary contraction on both sides, the direct and indirect, or consensual, reactions. Thus, in a patient with a complete lesion of one optic nerve the direct reaction to light is lost, but the pupil of the blind eye reacts consensually when a light stimulus is offered to the unaffected eye. Both direct and consensual reactions are impaired or lost in lesions of the constrictor fibres at any point in the third nerve, from the nucleus onwards, or in the ciliary ganglion and short ciliary nerves. In such cases the pupil will be dilated, due to the unopposed action of the dilator muscle, unless the cervical sympathetic is also paralysed.

The dilator fibres have their origin in the eighth cervical and first dorsal segments of the spinal cord, travelling to the muscle via the sympathetic chain, superior cervical ganglion, where the post-ganglionic fibres arise, sheath of the carotid artery, ophthalmic division of the fifth nerve, naso-ciliary and long ciliary nerves. Dilatation of the pupil can be produced in normal subjects by pinching the skin of the neck. Damage to these sympathetic fibres results in dilator paralysis and reduction in the size of the pupil. Fibres activating this system pass downwards from the hypothalamus through the brain-stem and cervical cord to the cells of origin. The signs of cervical sympathetic paralysis may be produced by lesions of the pons or medulla. The reflex activity of the pupil is unimpaired in lesions of this system.

Accommodation and convergence of the eyes are linked phenomena accompanied by pupillary contraction. This reflex is lost in lesions of the constrictor fibres at any point or in disease of the iris. Normally the pupils contract when one looks up and when the eyes are strongly closed.

PUPILLARY SIZE

Pupillary size is mainly determined by the degree of illumination, but it is subject to individual variation. There is a general tendency for the pupils to grow smaller with increasing age, and mobility may also be reduced in the elderly. The pupils are usually equal in health, but minor inequalities do occur in the absence of neurological or ocular disease; in such persons the reflexes are normal. Dilatation of the pupil is an important sign of a third nerve lesion, and here the pupillary changes and characteristic external ophthalmoplegia do not always develop *pari passu*. The pupils are enlarged in states of fear and physical pain, due to increased secretion of adrenaline. Atropine causes dilatation of the pupil by paralysing the parasympathetic fibres. Patients occasionally present with a fixed, dilated pupil due to contamination of the eye with atropine, during the preparation of hypodermic

injections, or with belladonna, as in belladonna liniment or mixtures. Cocaine causes enlargement of the pupil by stimulating the sympathetic dilator fibres. There may be great pupillary dilatation in hypoglycæmia. Contracted pupils are found in a variety of conditions, including neurosyphilis, disease of the pre-tectal region of the mid-brain, pontine hæmorrhage, cervical sympathetic paralysis, heat-stroke, instillation of eserine or pilocarpine, and morphine addiction.

In health the pupils are regular and circular in outline. Irregularity is commonly due to disease of the iris, but it also occurs when the light reflex is impaired, especially on the efferent side.

CLINICAL SIGNIFICANCE

The pupil in neurosyphilis.—The classical Argyll-Robertson pupil of neurosyphilis is small, irregular, fixed to light, reacting briskly on convergence but dilating incompletely to mydriatics. For the early diagnosis of neurosyphilis, however, it is important to suspect the patient with pupils which react imperfectly to light but well on convergence; in such a case the abnormality may be unilateral, and the abnormal pupil may be smaller or larger than its fellow. Pupils with some of the features of the Argyll-Robertson variety may be found in alcoholism and diabetes mellitus (so-called pseudo-tabes).

The myotonic pupil.—The pupillary abnormality found in this condition may be confused with that due to neurosyphilis. In the early stages the affected pupil is larger than the spared one, the reaction to light is lost, and the response to accommodation is slow or tonic. Later the affected pupil tends to become smaller, and ultimately the other eye may be involved. Various tendon reflexes are lost. Although there is no relationship between the syndrome and neurosyphilis it is wise to confirm clinical opinion by having a blood Wassermann reaction performed.

Cervical sympathetic paralysis (*Horner's syndrome*).—This is one of the common causes of pupillary inequality. A thorough search should be made for disease on the pathway previously described. The cause of an isolated Horner's syndrome not infrequently eludes the investigator.

Head injury.—Traumatic mydriasis may result from direct damage to the eye, as for example in boxers. Minor inequalities are found in some patients with concussion, possibly due to brain-stem damage. The appearance of a fixed dilated pupil on one side is an important sign of cerebral compression from epi- or sub-dural hæmorrhage.

Raised intracranial pressure.—One or both pupils may be dilated and fixed when the intracranial pressure is greatly raised by some form of space-occupying lesion, such as blood clot and other collections of fluid, abscess or neoplasm. The sign is a grave one.

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NOTES AND QUERIES

Deafness in Infants

QUERY (from a reader in Africa).—I was recently asked to see a male child aged 18 months whose mother contracted rubella in the second to third month of the pregnancy. She was worried because he did not speak. It seemed to me that the child was deaf and I referred him to an E.N.T. specialist who replied: 'I think there is no doubt a severe degree of deafness is present. The cry is typical. No cochleo-palpebral reflex was present but he seemed to respond to the higher-tone tuning forks, higher tones in the audiometer and also amplified speech. Accordingly I think he probably has some islands of hearing remaining and with teaching in a special centre it might be possible to develop this. He seemed intelligent and I did not think it was a primary mental deficiency'. He thought 'the age of 3 is about the earliest that one can legitimately start these children at a special school'.

(1) Can the child not start before 3?

(2) How long must the child remain at the centre? The parents are contemplating the mother returning to the United Kingdom with the child for treatment. But I am reluctant to support this suggestion.

REPLY.—The absence of the cochleo-palpebral reflex may indicate the presence of a fair amount of hearing, especially as the child appears to respond to higher tones. As the child has sound put within his reach so that it becomes loud enough to acquire meaning, he will learn to hear and as a result, over the course of the next two years or so, there will be an apparent improvement in his hearing. To a large extent the training and teaching of the meaning of sounds to the child can be done by the mother as is the case with the normally hearing child. The mother should talk close to the child's ear and any sound produced by the child should be repeated with encouragement by the mother so that the child may have an incentive to make further sounds. An attempt should be made to understand the sounds that the child is producing and if there is any resemblance to known words then they should be turned into those words. Every incident in a child's life can be used for this purpose, such as his meal times, or going for walks, or going to bed, or playing with his toys. It would be helpful to know how the mother at present communicates with the child and what sounds the child is producing; does he babble and does he produce continual sounds?

(1) It is important that the child's mother should start the training as soon as possible. The reason for this is that the deaf child learns best, as does a normal child, during the normal physiological period of learning which is present during the first three years of life. A long period of listening is necessary during which time the child learns first to recognize sounds and then to interpret their meaning. It is only when he can do this that he will start to talk. The child will only learn to do this if the sounds are loud enough, i.e. said in the ear, or said through a hearing-aid, said often enough and in association with their meaning, and by someone who is giving individual attention to the child.

(2) The answer to this obviously depends upon knowing the diagnosis, an assessment of the child's hearing, and the child's personality as a whole. The hearing loss and deafness due to rubella is very often of a flat type and if the higher frequencies are present I think it is possible that the lower ones are also, and it is reasonable to suppose that this child could learn to talk through his hearing.

The mother could go with the child for a period of, say, a month or six weeks to the Hostel at Ealing, but it seems a long way to come even though I feel sure we could give them the answer at the end of this time. I feel, however, that if we could have a few more answers as to where the child hears sounds—the distance, the type of sounds, where he hears the voice, if he turns for his mother's voice, if he turns for his familiar toy sounds (e.g. rattles, or a bell, or drum), what sounds are made by the child, how he attracts attention—perhaps we could start some training by postal tuition and so save what obviously would be a very drastic step in bringing the child over to this country.

On the evidence given I should not have thought this child was deaf enough to require education in a school for the deaf. On the contrary I should think he almost certainly has enough hearing to be able to hold his own in an ordinary school if the mother starts early home training on the right lines.

EDITH WHETNALL, M.S., F.R.C.S.

Hallucinations in the Aged

QUERY.—I have an old lady, aged 75, who for the past twelve months has suffered from visual hallucinations: people darting at her from the surroundings every day as soon as lights are dim. She has myxœdema which appears to be controlled by thyroid, 2 grains (120 mg.) daily. She is not hypertensive and there is no obvious arteriosclerosis (fundi and limbs). She has no other mental symptoms.

REPLY.—Visual hallucinations are not uncommon in the aged. They are often isolated

manifestations which do not necessarily increase in severity nor do they herald any psychotic illness. Thus, in general they have not the same serious significance as in a younger person with, for instance, schizophrenia.

The usual cause is thought to be arteriosclerotic changes in the brain, but the degree of mental disturbance bears little relationship to the extent of brain damage or to the severity of arteriosclerosis elsewhere in the body. Visual hallucinations can also be due to myxœdema ('myxœdema madness') and to intoxication with certain drugs, notably bromides. In myxœdema the mental symptoms are often prominent even though only mild hypothyroidism exists without any other gross abnormal signs. It would therefore be worth increasing the dose of thyroid to 3 grains (200 mg.) daily, at least temporarily, to see if her condition improves. Ophthalmic examination is also advisable to exclude any condition which might lead to misinterpretation of visual stimuli.

The question does not state to what extent the hallucinations are distressing to the patient or if her behaviour is giving concern to the relatives. As there are no other mental symptoms, it is probable that no treatment is indicated. If her hallucinations become so severe as to lead to markedly disturbed behaviour, then chlorpromazine, 25 mg. three times a day, should be tried.

A. N. EXTON-SMITH, M.D., M.R.C.P.

Piperazine in Ascariasis

QUERY.—I believe 'antepar' elixir (piperazine citrate) is the safest medicine for treatment of roundworm infestation. After administering the piperazine at bedtime is it necessary to give a purgative on the following morning? What is the safest purgative for a child and an adult, and in what quantity? If milk of magnesia is given, how much, and should it be diluted? Can castor oil be given after piperazine and has it any bad side-effects? If the worms die and are not expelled can there be any toxic reactions due to their putrefaction? Some patients say they get fever after piperazine treatment. What is the cause?

REPLY.—Piperazine citrate ('antepar' elixir; 'helmazine' elixir) is a safe medicine for the treatment of ascariasis. A single dose should be given just before the evening meal: 16 ml. for children weighing less than 40 lb. (18 kg.); 24 ml. for older children and adults. Fasting and purging are unnecessary, but in costive cases a saline purge, such as saturated sodium sulphate (60 ml.) or, for children, magnesium hydroxide mixture B.P. (2 to 8 ml.) may be given next morning. Fear of absorption has set tradition against castor oil after anthelmintics.

No toxic effects are to be expected even if there is delay in passing roundworms, and other causes should be sought for any fever after taking piperazine citrate.

E. LL. LLOYD, M.B., D.T.M.&H.

Chlorothiazide and Magnesium Excretion

QUERY.—Does chlorothiazide cause a significant loss of magnesium?

REPLY.—I know of only one report on the effect of chlorothiazide on the urinary excretion of magnesium (Robinson *et al.*, 1958, *Circulation*, **18**, 771). In a preliminary communication these workers report that in normal subjects 0.5 g. of chlorothiazide orally may increase urinary excretion of magnesium twofold.

R. I. S. BAYLISS, M.D., F.R.C.P.

Poisonous Berries

QUERY.—Could you please tell me which of the common berries found in gardens and hedges are poisonous? Children are often brought to me by their parents, with samples of the offending berries, and as I do not know which are poisonous and which are not, I have to wash out more stomachs than I presume is necessary.

REPLY.—In this country most garden berries and seeds are not poisonous. Many, such as the bright red berries of the black bryony (*Tamus communis*) or the fruits of the holly or of the hawthorn, at worst produce emesis. Those berries and seeds (wild and ornamental) which at times are credited with causing death include the black berry, fruit of the baneberry (*Actæa spicata*), as well as that of the white baneberry (*A. pachypoda*) and red baneberry (*A. rubra*) of the United States, the small sweet black but lethal fruits of *Coriaria myrtifolia* and the black berries of privet (*Ligustrum vulgare*); deadly nightshade (*Atropa belladonna*) and pokeweed (*Phytolacca Americana*), the red berries of mezereon (*Daphne mezereum*), the scarlet berries of the cuckoo pint (*Arum maculatum*) and the bright red cherry-like berries of the popular Christmas greenhouse plant, the Jerusalem cherry (*Solanum pseudo-capsicum*); the highly lethal seeds of the laburnum (*L. anagyroides Medic*) which in their pods might look like unusual peas in pods, or those of hemlock (*Conium maculatum*) used by mistake instead of anise seed, or the seeds or unripe capsules of the thorn apple (*Datura stramonium*), and finally the fruit of the horse chestnut (*Aesculus hippocastanum*) commonly called a conker.

S. LOCKET, M.B., B.S., M.R.C.P.

Rabies Contamination

QUERY (from a reader in India).—Could you please tell me whether the saliva of a patient suffering from rabies is infected, and also whether persons who have ingested food contaminated with saliva of a rabies patient should be inoculated with anti-rabies vaccine?

REPLY.—The saliva of persons suffering from rabies contains the virus in rather low concentration. Man-to-man infection is theoretically possible but, so far as I am aware, no proven case has been reported.

The answer to the second part of the question depends upon the degree of contamination. Although rabies virus can pass intact mucous membrane it is seldom possible to infect animals by allowing them to feed on rabid material. It would therefore seem unjustifiable to embark on a course of vaccine therapy with its attendant discomfort and risk, unless the ingested food was grossly contaminated with undoubtedly infected saliva, in which case surely no-one would voluntarily eat it.

D. R. SEATON, M.B., M.R.C.P., D.T.M. & H.

English Spas in Winter

QUERY (from a reader in Eire).—Would you let me know where a patient of mine could go in England for a holiday at this time of year and have the benefit of spa treatment (hydrotherapy and/or physiotherapy)?

REPLY.—At this time of year, choice is, if not dictated, at any rate influenced by climatological considerations. It would be of advantage to know what is the inquirer's idea of a 'holiday'—a quiet resort that is acceptable to one inspires boredom in another who looks for amusements and distractions. To what extent are hydrotherapy and physiotherapy desired or required? In this particular instance it would appear to be comparatively unimportant rather than a dominating indication. I think it is safe to recommend Bournemouth or Torquay as suitable whatever the patient's disposition, and as providing all that can be required medically. Sidmouth is satisfactory climatically, but the resources of a 'spa' are not available to the same extent and it would appeal only to those requiring a 'quiet' holiday.

SIR ADOLPHE ABRAHAMS, O.B.E., M.D., F.R.C.P.

Rabies in Norfolk

MR. J. F. D. TUTT, F.R.C.V.S., of Winchester, writes:—The article on 'Rabies in Norfolk' by Dr. P. S. Barclay in the November issue (p. 626) interested me as the area he describes is well known to me and as I am probably one of the few who actually saw the last few cases of rabies in a dog in this country. Shortly after coming here in 1919 I had two cases: one in a Labrador retriever, the other in an Aberdeen terrier. The former showed no propensity to bite, the only symptoms being profuse salivation and eating objects such as its bedding. The terrier, on the other hand, ran off from its home in an excitable state, snapping at passers by, and in one instance tried to drag a woman off her bicycle. Strange to relate it returned home, and when seen by me some time later had developed paralysis of the lower jaw, accompanied by profuse salivation. Both animals were destroyed and laboratory examination confirmed the diagnosis of rabies.

The owner of the Aberdeen terrier had to go to the Pasteur Institute for treatment, as a precautionary measure, as she had allowed the animal to lick her hand which had a small wound on it. She did not develop rabies but, curiously enough, it reduced her bulk, which was like that of Tessie O'Shea, to one more like that of a modern fashion model.

PRACTICAL NOTES

Mepacrine in Petit Mal

ATTENTION is drawn by R. A. Miller (*Scottish Medical Journal*, 1958, **3**, 441) to the value of mepacrine in the treatment of petit mal. He reports his findings in 16 children, aged 5 to 12 years, all of whom had petit mal for periods ranging from four months to four years which had not responded satisfactorily to various anticonvulsive drugs. The dosage was 100 mg. daily from Monday to Friday each week for three months to two years. At the end of this period, 10 of them still had symptoms sufficiently severe to justify a modification of treatment and, in addition to the mepacrine, they were given 200 to 400 mg. of meprobamate daily for five days a week. After one or two months of this therapy, meprobamate was replaced by troxidone (0.3 g. twice or thrice daily). There was only one case which did not respond to mepacrine, whilst six had no fits, eight improved with fits occurring less than eight times a day, and one showed only slight improvement. Of the nine patients showing improvement, the combination of meprobamate and mepacrine was followed by the reduction of attacks to less than

two a day in four. The remaining five children were given the troxidone-mepacrine combination which resulted in the reduction of attacks to less than two daily in each case. All these five children had previously been given troxidone alone, and in three it had failed to produce any improvement, whilst in two it had produced only temporary improvement. Two difficulties were encountered with the use of mepacrine: one was yellowish discoloration of the skin; the other was the production of grand mal attacks in two patients.

Precordial Murmurs in Pregnancy

ATTENTION is drawn by J. W. Hurst and his colleagues (*New England Journal of Medicine*, September 11, 1958, **259**, 515) to the fact that 'a variety of innocent murmurs may develop during pregnancy and are often attributed to heart disease'. They give details of two illustrative cases. One was a 21-year-old woman who was found to have a precordial systolic murmur, heard with maximum intensity just to the left of the mid-sternum. A palpable artery was found in the third left intercostal space near the sternum, occlusion of which with the finger caused the murmur to disappear immediately. It was concluded that the murmur was due to a bruit in a branch of the mammary artery arising as a result of the enlargement of the artery and its branches during pregnancy. The unusual feature in this case was that the murmur persisted after delivery and did not disappear until the baby was weaned from the left breast. The second case was an 18-year-old primigravida who was referred to hospital in the eighth month of pregnancy because of suspected congenital heart disease. She was found to have a loud continuous murmur audible in the 2nd and 3rd left intercostal spaces, which had originally suggested the diagnosis of patent ductus arteriosus. It was found, however, that the murmur could be altered by firm pressure with the stethoscope bell, and that it was abolished by light pressure between the pulmonary area and the breast. The murmur had disappeared when the patient was seen a month after delivery. It was concluded that the murmur was due to a large volume of blood flowing rapidly through the large dilated superficial veins during systole and diastole.

Auscultation of Intracardiac Thrombi

AUSCULTATION with a small-belled stethoscope lightly applied over the right carotid artery is of value in the bedside diagnosis of left-sided intracardiac thrombi, according to H. H. Berg (*German Medical Monthly*, October 1958, **3**, 320). He gives details of four cases to support his suggestion—in all of which there was post-mortem confirmation of the diagnosis. In two cases, in both of which necropsy revealed polypoid or racemose thrombotic masses arising from an ulcerated cusp of the aortic valve, a rough and constant systolic murmur was heard: in the more acute case it was audible only over the right carotid artery. The third case was a man, aged 71, with severe myocardial failure and gallop rhythm following a myocardial infarction. Over the right carotid artery a 'peculiar drumming (staccato)' sound, about twice the frequency of the gallop rhythm, was heard. It is described as resembling that produced by 'a piece of dry brushwood run over the spokes of a bicycle'. It was considered to be due to an intracardiac flapping thrombus at the site of infarction—which was confirmed at necropsy. A similar, but less constant sound was audible over the right carotid artery in the fourth case. Its variability was attributed to the changing position of a mural thrombus in the ventricle. This diagnosis was confirmed by the development of embolic phenomena and the post-mortem finding of 'a freely mobile intracavitary fragment'.

Gastric Secretion in Pernicious Anæmia

As a result of his findings in 79 patients with pernicious anæmia, A. Jacobs (*British Journal of Hæmatology*, October 1958, **4**, 465) concludes that 'there are no absolutely characteristic changes in the secretion of acid by the stomach in pernicious anæmia. The absence of achlorhydria does not necessarily exclude the diagnosis'. Using an electrometric method of measurement of pH, he found an increase of acidity of 1 pH unit or more following histamine stimulation in 35 patients. In only 23 cases was the rise in acidity of the gastric contents less than 0.5 of a pH unit. Whilst most patients secreted only a small amount of acid, 'all degrees were found from complete absence of acid secretion to presence of "free acid" in one case'. In another series of 100 consecutive histamine test meals performed on patients with pernicious anæmia, the author found 39 in whom the 'total' acid following histamine stimulation was more than double the maximum value before histamine. This increase is due to a degree of acid secretion insufficient to change the colour of Töpfer's reagent. He concludes: 'In "atypical" patients in whom acid secretion is unusually high and "free" acid is present, it is on the measurement of intrinsic-factor secretion alone that the diagnosis of pernicious anæmia can be firmly based. These cases differ from typical ones only quantitatively, and it may

be that they represent an early stage in the development of the disease'.

White Cell Count in Uræmia

LYMPHOPENIA is a striking feature of acute uræmia, according to O. Jensson (*British Journal of Hæmatology*, October 1958, **4**, 422) who bases his conclusion upon his findings in 14 patients with acute renal failure. In most cases the lymphopenia was accompanied by a neutrophil leucocytosis and a tendency for the nuclei of the polymorphonuclears to be hypersegmented. This neutrophil leucocytosis occurred irrespective of the presence of obvious infection. In three patients marrow obtained by sternal puncture showed myeloid hyperplasia. There did not appear to be any correlation between the degree of lymphopenia and the level of the blood urea. Lymphopenia was also found in 40 cases of chronic uræmia. Whatever may be the prognostic significance of lymphopenia in chronic uræmia—and this has been said to be ominous—in this series of cases of acute uræmia the lymphocyte count gave no indication of the ultimate outcome and was of no help as a guide to the use of hæmodialysis. 'It seems', the author says, to be 'but a sign of serious renal failure, quite unrelated to its cause or the possibility of recovery'.

An Efficient Laxative

BISACODYL (di - (*p*-acetoxyphenyl) - 2 - pyridylmethane; 'dulcolax'), according to A. Brassinne (*Revue Médicale de Liège*, October 15, 1958, **13**, 686) is an effective non-irritating laxative which is well tolerated by patients. This conclusion is based upon his findings in a series of 106 cases of constipation, 48 men and 58 women, three-quarters of whom were over the age of 40. There were 24 cases of occasional constipation, 74 cases of chronic constipation, and eight who could not be definitely allotted to either of these categories. All were outpatients. The dosage was 5 mg. in 16 cases, 10 mg. in 79 cases, 15 mg. in six cases, and 20 mg. in five cases. The results were 'excellent' in 71 cases and 'moderate' in 20 cases. In this latter group six complained of persistent hard motions and 14 of a certain amount of colic. Fifteen cases are classed as failures: 10 because of no improvement in the degree of constipation, and five because the colic induced by the drug was so severe that treatment had to be discontinued. It is recommended that the drug be given at night on going to bed. In 74 of the 86 patients in whom it was given at this time, sleep was not disturbed, and there was a movement of the bowels eight to ten hours later. In only four patients was sleep disturbed—a bowel motion occurring four to six hours after taking the drug. In the remainder there was a lag period of more than fourteen hours.

Blepharospasm

IN the management of cases in which blepharospasm renders adequate examination and treatment difficult, P. A. Graham (*British Journal of Ophthalmology*, October 1958, **42**, 589) has found a benzocaine-urethane solution of value. This solution depends for its action on the property of urethane in preventing crystallization of a saturated solution of benzocaine within certain limits of concentration. When the solution is diluted by tissue fluids, however, crystalline benzocaine is deposited in the tissues, giving rise to a depot, the action of which, though localized, persists over a prolonged period. The solution is prepared by adding crystalline benzocaine to a 40% solution of urethane in distilled water in the proportion of 2%, gentle heat being used to dissolve the benzocaine. After standing for twenty-four hours the solution is filtered and sterilized by autoclaving. This solution is stable, easily prepared in a hospital dispensary, remains sterile and is said to have 'no serious side-effects in the dosage used, even if accidental intravenous injection should occur'. The injections are made just below the condyle of the mandible, care being taken to insert the needle right down to the periosteum. Normally, three depots of 0.5 ml. are sufficient. As the solution causes some pain immediately after injection, 1.5 to 2 ml. of procaine are injected as a preliminary procedure; this may produce an immediate, though temporary, complete facial paralysis.

Sterile Eye-drops

IN 1955, a dispensary and sterilization committee was set up to supervise methods of preparing and sterilizing eye-drops and eye-lotions at the Moorfields Hospitals. The methods now in use are described in detail by Frederick Ridley in the *British Journal of Ophthalmology* (November 1958, **42**, 641). Only some of these can be referred to here. For full details the reader is referred to the original article. The first essential stressed is the use of screw-cap drop-bottles, which secures freedom from evaporation and protection of the lip of the bottle. Equally important is the use of an effective protective substance in all drops. The two protective substances used at Moorfields are methyl hydroxybenzoate (0.1%) and phenylmercuric nitrate (0.004%). Over a three-year period very few cases of dermatitis medicamentosa due to either of these preservatives have been encountered. To prevent cross-infection among patients it is essential that individual drops must be provided for each patient. Repeated bacteriological testing

of drops that have been in use in the outpatient department and the casualty ward has shown that they are still sterile and self-sterilizing after three months. To be on the safe side, however, all drops are replaced at the end of one month.

Trochanteric Syndrome

THE tronchanteric syndrome is the analogue of 'bursitis' of the shoulder and often 'masquerades as sciatica', according to M. H. Leonard (*Journal of the American Medical Association*, September 13, 1958, **168,** 175). Its frequency is indicated by the fact that during the period 1955-57, he saw 18 cases, which represented approximately 0.1% of the patients seen in private orthopædic practice. The onset is often sudden, with pain on the lateral aspect of the hip, radiating down the posterolateral aspect of the thigh. Those movements which relax the abductors of the thigh (passive abduction and external rotation) tend to diminish the pain, whereas those which tighten these muscles (passive internal rotation and abduction) increase it. A gluteal limp is often present. The most constant and useful finding is local tenderness over the trochanter major. The principal etiological factor is said to be 'wear and tear rather than a single insult'. The structures involved can include the tendons of the gluteus maximus, gluteus medius and gluteus minimus, and the bursa separating these tendons from the trochanter major. In all his cases the author has obtained complete relief from infiltration of the tender areas with local anæsthetic followed by hydrocortisone in doses of 25 to 100 mg. In some cases the condition may be due to the presence of extraneous material such as a hip nail; in such cases the 'foreign body' should be removed.

Streptomycin Dermatitis in Nurses

IF no precautions are taken one case of streptomycin dermatitis develops among nurses for approximately every 4000 injections given, according to H. T. Wilson (*Nursing Times*, November 28, 1958, **54,** 1394). The sites most commonly affected are the sides and backs of the fingers, the backs of the hands, the forearm, elbow flexures and face, particularly the eyelids. Of over 20 cases which the author has investigated, three were so severely affected that they had to give up nursing. Confirmation of the diagnosis is obtained by patch testing: a square of white lint, 1 cm. in diameter, is soaked in a 5% aqueous solution of streptomycin, placed on the back, covered with cellophane and secured with 'elastoplast'. This is removed in forty-eight hours, and in positive cases there is an area of redness usually associated with œdema and sometimes with small vesicles. In the author's experience, once a nurse has acquired a high degree of sensitivity she can seldom handle streptomycin again, and he has known only one nurse who lost her sensitivity spontaneously—about two years after onset of the rash. In the case of a nurse who cannot avoid handling streptomycin, desensitization is worth considering. All of the six nurses in whom the author attempted desensitization responded satisfactorily but two relapsed after a year—one partially and one completely. Prevention is better than cure, however, and streptomycin dermatitis rarely develops when nurses wear gloves and masks during injection of the antibiotic. In two wards of a London hospital in which these precautions were observed, approximately 100,000 injections of streptomycin were given over a period of eight years without a single case of dermatitis among the nursing staff. During the same period some 40,000 injections of streptomycin and 25,000 injections of 'crystamycin' were given elsewhere in the hospital where masks were not worn, and gloves only occasionally, and 14 nurses developed streptomycin dermatitis.

Apples and Dental Disease

AN apple a day may not keep the doctor, but it may help to keep the dentist, away judging from a report by G. L. Slack and W. J. Martin (*British Dental Journal*, November 18, 1958, **105,** 366), based upon their findings in a group of 171 children, 90 of whom were given apples to eat after every meal and after eating anything between meals; the remaining 81 acted as a control group. At the end of two years the incidence of gum disease was significantly lower in the apple group than in the control group. The incidence of caries was also lower in the apple group, but caution is necessary in the interpretation of the significance of this as before the investigation started the incidence of caries was higher in the control group than in the apple group and there is therefore a possibility that the children in this group were more susceptible to caries than those in the apple group. It is concluded that 'the results of this pilot study lasting two years indicate that a large-scale study for a longer period would be worthwhile'. It is stressed that 'only apples that have crisp firm flesh can be considered as an aid to oral hygiene'. The action of the apples appears to be twofold. The flow of saliva is stimulated by the low pH of the apple and the mastication of the fibrous apple fragments, whilst 'the mechanical cleansing action of the apple sweeping over the teeth and gums in the presence of increased saliva flow removes debris and stimulates the gum tissues'.

REVIEWS OF BOOKS

Clinical Hæmatology in Medical Practice. By G. C. DE GRUCHY, M.D., F.R.A.C.P., M.R.C.P., M.C.P.A. Oxford: Blackwell Scientific Publications, 1958. Pp. xii and 620. Illustrated. Price 50*s*.

THIS book is stated to bridge the gap between the inadequate descriptions of blood diseases found in textbooks of general medicine and the comprehensive hæmatological reference books and monographs. Although neither a small book nor a particularly cheap one, it does achieve this objective very successfully. It is indeed an excellent book for the general physician and the postgraduate student. It gives a lucid and up-to-date account of the subject and, although not claiming to be comprehensive, there can be little of importance to the clinical hæmatologist that it does not deal with. Throughout, the emphasis is on the clinical and practical rather than laboratory or academic point of view, and the style is acceptably dogmatic. A feature is the insertion of useful synoptic tables. The text is adequately illustrated with monochrome photographs and charts, but no attempt is made to provide colour pictures or anything along the lines of an atlas. In this the author is very wise. Nor is there any attempt at a comprehensive bibliography, but at the end of each chapter there is a selected list of references.

Perusal of the book revealed no grounds for criticism either under the heading of commission or omission, and proved an enlightening task for the reviewer. It left him full of admiration.

Diseases of the Esophagus. By J. TERRACOL and RICHARD H. SWEET. Philadelphia and London: W. B. Saunders Co., 1958. Pp. xiii and 682. Figures 409. Price £7.

SEVERAL years ago Dr. Richard H. Sweet, Associate Professor of Surgery, Harvard Medical School, conceived the idea of writing a book on the œsophagus and its diseases, for, to quote his own words, 'there was no comprehensive authoritative book . . . in the English language'. In 1952, however, he discovered that the task of writing a comprehensive treatise had already been accomplished by Professor Terracol, of Montpellier, and his colleagues. As a result of this discovery, Dr. Sweet changed his original idea into that of translating Terracol into English, thereby, as he says, making the vast store of information which it contains accessible to English readers, and at the same time revising and modifying it to include some of the newer knowledge, particularly regarding surgical treatment. What strikes one as being very odd is that the references taken from M. Terracol's book are in French, whereas the references that Dr. Sweet has added are in English. Further, when a reference is taken from a French source by Dr. Sweet which did not appear in the original Terracol, the title is given in French, and followed by an English translation! These criticisms may be regarded as trivial, but they cannot readily be overlooked, for their presence detracts from the enjoyment of the book, and in some way also from a feeling of confidence in the American version of the text as a whole.

Throughout the sections translated from the French one finds many details to which exception may be taken, and many ideas which are not in accordance with modern thought or knowledge. On p. 19 we read the equivocal statement: 'It (the diaphragmatic canal) is more nearly an extrinsic sphincter mechanism (if it has any sphincter-like action at all) similar to the relation of the levator ani muscle to the rectum', a description calculated to confuse rather than clarify. The term 'cardiospasm' is deliberately abandoned, and replaced by 'mega-esophagus'. But surely the latter is the result of spasm, and most cases of cardiospasm are seen and treated before a mega-œsophagus develops. The Terracol-Sweet opinion is that the disturbance is not at the cardia, and yet Heller's operation is recommended. One searches eagerly but in vain for an account of the problem of insufficiency of the cardia associated with hiatus hernia. Reflux associated with the latter is not even mentioned as a cause of œsophagitis. The whole matter seems to be ignored—a rather astonishing omission having regard to the attention that has been given to the subject during the last decade. The best parts of the book, as one might expect, are among those that are new, and not among those rehashed from the French. The chapter on cancer of the œsophagus, written with the authority of a master of the subject, is perhaps the best section.

Whilst appreciating the value of making M. Terracol's splendid book available to a much larger audience one cannot but regret that Dr. Sweet did not carry out his original intention of writing a comprehensive work from start to finish himself. Perhaps he may yet do this.

Modern Trends in Surgical Materials. Edited by LEON GILLIS, M.B.E., M.CH., F.R.C.S., F.R.C.S.ED., D.L.O. London: Butterworth & Co. (Publishers) Ltd., 1958. Pp. xi and 275. Illustrated. Price 72*s*. 6*d*.

THE increasing use of synthetic and natural substances for implantation in the human body and for numerous appliances associated with surgery and dentistry makes this a most

interesting and timely publication. The contributors are all well-known experts in their own fields and more than a third of them are scientists rather than clinicians, who are able to present the scientific background of many materials with which the practising surgeon is all too unfamiliar. Indeed it is this aspect of the book which makes it so absorbingly interesting and valuable. The book will appeal mainly to orthopædic surgeons concerned so much with metallic and plastic implants but it should also be read by surgeons interested in technique, as all should be. It is made quite clear by the authors that perfection has by no means yet been achieved in the use of synthetic and natural implants, but the book provides a concise summary of the present state of knowledge in a rapidly advancing subject.

Inevitably with such a wide, and indeed novel, subject there are gaps where the general surgical reader would wish to know more, and in some respects the substance of the work is ill-balanced. For example, although appliances for ileostomy and colostomy are described and vascular prostheses given detailed consideration, there is no mention of any genito-urinary appliances or of the materials of which urethral catheters are best made. Some mention might have been made of the properties of surgical dressings and transfusion tubing which would perhaps be of more general interest than the raw materials used in the construction of artificial limbs. The chapter on abdominal surgery does not always follow accepted British practice; its author favours the use of stainless steel wire as a suture material though this substance receives no mention at all in the chapter devoted to suture materials and one tends to feel perhaps a little old-fashioned when reading that linen thread is not now often used in ordinary surgical procedures. Fascial grafts are dismissed in four lines. The chapter on sterilization, however, is first-class and of much current importance. Minor criticisms do not detract from the concept and value of this book devoted to surgery in this 'plastic age'.

Behaviour and Physique. By R. W. Parnell, M.D., M.R.C.P. London: Edward Arnold (Publishers) Ltd., 1958. Pp. viii and 134. Illustrated. Price 28*s*.

During the last ten years Dr. Parnell has published a stimulating series of articles on the value of somatotypes. In the course of this work he has evolved his own method of somatometry which is now widely accepted as a more practical alternative to the cumbersomely intricate method of Sheldon in the United States. Parnell's alternative may not be as scientifically precise as that of Sheldon, but it has the great practical advantage of being simpler and requiring a minimum of measurements, all of which can be recorded accurately by the ordinary observer. What it loses in precision is more than compensated for by what it gains in practicability.

In this book he describes his method in detail and then goes on to discuss its applications. The most important of these may well be in the field of mental health, particularly as a means of detecting the individual who is unlikely to be able to stand up to the strains and stresses of life, and there is much new data in his book on the investigations into this field which he is carrying out in conjunction with Dr. Ian Skottowe. Of equal interest to many readers will be the account of its application in assessing intelligence, academic aptitude and character traits in children. In many respects this is the most stimulating medical book of the year.

Recent Advances in Cerebral Palsy. Edited by Ronald S. Illingworth, M.D., F.R.C.P., D.P.H., D.C.H. London: J. & A. Churchill Ltd., 1958. Pp. x and 389. Illustrations 136. Price 50*s*.

The editor has thirteen other contributors to help him in this review of a highly topical subject. The sections on treatment (drugs, physical therapy, orthopædic surgery and neurosurgery) are especially good and justify in great part the term 'recent advances'. Chapters on the psychological aspects and educational problems likewise reflect modern views. The editor's own contributions are in some ways less successful. His suggested classification is too simple and excludes involvement of the muscles supplied by the bulb so that a laryngeal stridor in young babies is not discussed. (Double hemiplegia will cover this.) More difficult to accept is that he does not face in any detail the problems of 'tone' whereas some neurologists feel that this is the key to classification. Indeed the word does not occur in the index which is in any case very poor by any standard and certainly by that usually set by the publishers. Professor A. W. G. Ewing contributes a good chapter on deafness in cerebral palsy and speech therapists at the Sheffield Children's Hospital give an encouraging account of their methods. Professor Norman Capon has written a characteristically charming foreword.

Fractures and Dislocations. By George Perkins, *M.C.*, M.Ch., F.R.C.S. University of London: The Athlone Press, 1958. Pp. 363. Figures 255. Price 57*s*. 6*d*.

This is an instruction manual comparable in its style and scope with that issued with a new Rolls-Royce car. It assumes that the reader is interested and intelligent. In reading it the

attention of the reader must not wander for an instant for fear of losing the thread of the argument and so missing the point of discussion as it is logically unfolded. It would be hardly accurate to describe this book as a standard work on fractures and dislocations. It should be found in the hands of the surgeon who knows the standard practice and who wants to improve his treatment. This book is for the perfectionist who is only satisfied with the best. Profusely and aptly illustrated, it is written in an acceptable style with brief sentences and without display or unnecessary words. It is easy to read but it is deceptively full of meaning.

This is not just another book on fractures, it is *the* book on fractures. Americans especially could profit from it.

General Diagnosis and Therapy of Skin Diseases. By H. W. SIEMENS, M.D. (translated from the German Edition, 1952, by Kurt Wiener, M.D.). Chicago: The University of Chicago Press; London: Cambridge University Press, 1958. Pp. vii and 324. Figures 375. Price 75*s*.

WITH the bewildering developments in the science of medicine there is a tendency to neglect the art—an eventuality that would be particularly unfortunate in dermatology. It is salutary, then, to read this book (and it is meant to be read rather than dipped into—it is not a conventional textbook) which concentrates on clinical and practical aspects and teaches basic principles as the guide to accurate diagnosis and effective treatment. The author's aim, in other words, is to train the dermatological eye. An introductory chapter on anatomy and histopathology is followed by sections describing in minute detail the colour, the lesions (level, deposits), distribution (arrangement, site), consistency, hair, nails, mucosæ, systemic signs and symptoms, subjective symptoms and history, and auxiliary diagnostic techniques. The second part consists of the principles of therapy. There are chapters on the vehicles, medications in the stricter sense (active ingredients), the administration of the treatment, physical therapy, minor surgery in skin diseases, systemic treatment, and finally a critical appraisal of therapy in the light of experience. Professor Siemens complains that some dermatologists think it beneath their dignity to concern themselves adequately with external therapy. He teaches the importance of individualization, the use of only what experience has shown to be effective, the careful weighing of effect against toxicity, distrust of complicated prescriptions, no matter how famous, and of medications chosen on pharmacological expectations, and that the first question to decide is whether to treat at all.

The book is profusely illustrated, and the hundreds of little photographs in black and white (mostly close-ups of elementary lesions) are first-class and have admirably concise explanatory legends. It is a fascinating book and no dermatologist—be he teacher, clinician or student—could fail to profit from Professor Siemens' presentation of his own precepts and meticulous methods.

An International Nomenclature of Yaws Lesions. By C. J. HACKETT, M.D., F.R.C.P. World Health Organization Monograph Series No. 36. London: H.M. Stationery Office, 1957. Pp. 104. Illustrated. Price 20*s*.

IN this attempt to standardize nomenclature the various stages of yaws are defined and described, and the division between early and late lesions is made thoroughly clear. The detailed nomenclature which is set forth here is a bold attempt to solve a difficult problem, but it remains to be seen whether it will ultimately prove to be a satisfactory solution. The description of the initial yaw as 'the papilloma' or as 'papillomatous' is an obvious weakness in the description of a disease which is characterized by papillomatous lesions in all its stages. Each variety of lesion is named and beside it are shown some of the more common synonyms, together with a brief clinical description of the lesion.

For the illustrations alone, the possession of this volume is an essential for all dermatologists, venereologists and experts in tropical diseases. It is likely to be particularly valuable in this country at the present time, where so many immigrants are arriving from areas where yaws is endemic. Dr. Hackett and his collaborators are to be congratulated on the production of a really valuable publication.

De Circulatione Sanguinis. By WILLIAM HARVEY. Translated by Kenneth J. Franklin. Oxford: Blackwell Scientific Publications, 1958. Pp. xxiii and 184. Price 22*s*. 6*d*.

PROFESSOR FRANKLIN'S latest masterpiece is a fitting sequel to his translation of 'De Motu Cordis'. In these later essays and letters Harvey reviews his life's work. He was 71 when he wrote the two essays and 79 when the last of the letters was written. His first public reference to the circulation was in a Lumleian Lecture in 1616. He published 'De Motu Cordis' in 1628 and 'De Circulatione' in 1649. During the 21 years that elapsed between these two publications there was, he says, 'scarcely a day, or

even the smallest interval of time passing, in which I have not heard both good and ill report of the circulation that I discovered'. We may therefore assume that 'De Circulatione' expresses his matured judgment on the significance of his discovery. These essays and letters are of even greater interest than the original publication for they illumine so brilliantly the working of his fertile mind, groping for the truth that he knew must underlie his discovery of the circulation, but which, as yet, was only half revealed. In Harvey the twin arts of observation and experiment were perfectly integrated: he learned the art of going deep and tracking the source of things to their subtlest retreats and he knew just when to wonder.

We owe a great debt to Professor Franklin for his felicitous translation and beautiful production of Harvey's two major works, which reveal so attractively the mind of a master scientist whose works, hitherto, had scarcely been sufficiently appreciated.

NEW EDITIONS

An Introduction to General Practice, by Denis Craddock, M.B., CH.B., D.OBST.R.C.O.G., in its second edition (H. K. Lewis & Co. Ltd., 42*s*.) has been expanded so that it has virtually become a 'textbook' of general practice rather than an 'introduction'. It can be as wholeheartedly recommended to the young general practitioner as the first edition, and there are many experienced practitioners who will learn much from its pages. With this book by his side the novitiate in general practice will be well on the way to an understanding of general practice which his seniors only acquired as a result of hard experience. Experience is still the keynote of good general practice but it will be acquired much more readily with Dr. Craddock's book as a guide.

Clinical Chemistry in Practical Medicine, by C. P. Stewart, D.SC., PH.D., and D. M. Dunlop, M.D., F.R.C.P., F.R.C.P.ED., in its fifth edition (E. & S. Livingstone Ltd., 27*s*. 6*d*.) admirably maintains the purpose for which this book was originally written: 'to treat adequately, within a small compass, the more everyday application of biochemistry to the problems of clinical medicine'. Written primarily for students in their clinical period, it is also the ideal book for the practitioner who wishes to maintain an intelligent interest in this important branch of diagnosis.

A Synopsis of Hygiene, by Llywelyn Roberts, M.D., M.R.C.P., D.P.H., in its eleventh edition (J. & A. Churchill Ltd., 60*s*.) has been entirely reset as well as thoroughly revised. As a guide to public health in the strict sense of the term it can be thoroughly recommended but, like so many books in this field, it fails to maintain the same standard when it impinges on the clinical field. This is particularly well exemplified in the paragraphs on folic acid and vitamin B_{12}. The section on vitamins is further blemished by two unfortunate spelling errors (p. 350). When the author sticks to his last, however, he is a sound guide and the new edition well maintains the high standards of its predecessors.

Hey Groves' '*A Synopsis of Surgery*', edited by Sir Cecil P. G. Wakeley, Bt, K.B.E., C.B., F.R.C.S., in its fifteenth edition (John Wright & Sons Ltd., 1958, 37*s*. 6*d*.) is a tabulated account covering the whole field of surgery in abbreviated style. It contains a vast amount of detailed information, made easily accessible by the system of headings and the excellent index. These qualities make it perhaps most suitable for purposes of revision and preparation for examinations. In addition to an extensive revision of existing material, the book now contains new sections on chemotherapy and antibiotics, and on cardiac and peripheral vascular surgery.

Black's Medical Dictionary, by William A. R. Thomson, M.D., in its twenty-third edition (A. & C. Black Ltd., 35*s*.) has undergone careful revision, many sections being rewritten, whilst new sections have been added on subjects such as steroid anæsthetics, artificial insemination, and tranquillizers.

Pathology for Students of Dentistry, by George L. Montgomery, T.D., M.D., F.R.S.E., F.R.C.P.ED., in its second edition (E. & S. Livingstone Ltd., 40*s*.) has been revised in the light of recent knowledge and the illustrations have been greatly improved. Professor Montgomery is to be congratulated on the balance of his subject matter. He takes the student easily through the basic elements of general pathology and stresses just the subjects which should be their main interest. There are no diagrams, line-drawings or summaries but reference is made easy by a good index and the skilful use of sub-headings and italics.

INDEX AND BINDING CASES

The index to Vol. 181 (July-December, 1958) is being forwarded to all subscribers with this issue. Binding cases for this and previous volumes are available in green cloth with gilt lettering, price 6*s*. each, post free. The cases are made to hold 6 copies after the advertisement pages have been removed; they are not self-binding. Alternatively, subscribers' copies can be bound at an inclusive charge of 15*s*. per volume; this includes the cost of binding case and return postage.

The contents of the February issue, which will contain a symposium on 'The Acute Abdomen,' will be found on page A 112 at the end of the advertisement section.

Notes and Preparations see page 137.
Fifty Years Ago see page 141.
Motoring Notes see page A 87.
Travel Notes see page A 91.

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"... a non toxic product which, in our opinion, is more active than other anti-angina preparations advocated to date."

Rev. Méd. Liège., 1957, 12, 157,

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Hyoscyamine Sulphate B.P.C. (1949)	0.0875 mg.	→ alleviates nausea and vomiting
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Phenacetin B.P.	130.0 mg.	→ relieves residual occipital pain

In a recent clinical article (J.A.M.A., 1957, 163, 1115) it was stated that in a series of 2,511 cases in which 28 agents were tested in the symptomatic treatment of migraine, ergotamine tartrate was proved to be the most useful drug—and 81% of the patients showed improvement when ergotamine tartrate and caffeine were compounded with belladonna alkaloids.

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NOTES AND PREPARATIONS

NEW PREPARATIONS

'BIOTEXIN SYRUP', each 5 ml. of which contains 125 mg. of novobiocin as the water-soluble monosodium salt, is an oral antibiotic which is 'especially effective' against *Staphylococcus aureus* even when this is resistant to other antibiotics. Available in bottles containing 60 ml. (Glaxo Laboratories Ltd., Greenford, Middlesex.)

'CALCIPEN V-SULPHA SUSPENSION' is a 'ready-prepared palatable preparation', each 5 ml. of which contain 60 mg. of phenoxymethylpenicillin as the calcium salt and 0.5 g. of sulphadimidine. It is said to be especially indicated in mixed infections and to be particularly suitable for children. Available in bottles of 60 ml. with 5-ml. plastic spoon. (Boots Pure Drug Co. Ltd., Station Street, Nottingham.)

'DEANER' tablets each contain 25 mg. of dimethylaminoethanol in the form of the para-acetamido benzoic acid salt, and are intended for the treatment of general debility, nervous fatigue, mild depression, chronic headache and migraine. Issued in bottles of 100 and 500. (Riker Laboratories Ltd., Morley Street, Loughborough, Leicestershire.)

'EQUADIOL' tablets each contain 200 mg. of meprobamate and 0.01 mg. of ethinylœstradiol and are indicated for the control of both the psychological and the physical aspects of the menopause. They are said to provide 'effective, well-tolerated œstrogen replacement plus safe selective sedation'. Issued in bottles of 20 and 100 tablets. (John Wyeth & Brother Ltd., Clifton House, Euston Road, London, N.W.1.)

'LAPUDRINE' tablets each contain 20 mg. of chlorproguanil hydrochloride, which is an antimalarial drug with properties similar to those of proguanil but more persistent. It is said to be well tolerated and to provide effective prophylaxis in a dosage of one tablet a week. Issued in containers of 200 (20 x 10) and 500 scored tablets. (Imperial Chemical Industries Ltd., Pharmaceuticals Division, Fulshaw Hall, Wilmslow, Cheshire.)

'ONYCHOPHYTEX' paint contains an antifungal compound, borottanic complex, in a penetrating vehicle of ethyl acetate and alcohol, and is intended for the treatment of onychomycosis. When applied, the paint 'dries to a colourless adherent film that is gradually dissolved by normal skin moisture, with slow and sustained release of the active ingredient'. Issued in bottles of 30 ml. with brush attached. (Savory & Moore Ltd., 60-61 Welbeck Street, London, W.1.)

'SOFRAMYCIN NEBULIZER' contains soframycin, 1.25%; gramicidin, 0.005%; and phenylephrine hydrochloride, 0.25%, in a buffered isotonic saline vehicle, and is intended for the treatment of acute coryza, rhinitis, nasopharyngitis and sinusitis. (Roussel Laboratories Ltd., 847 Harrow Road, London, N.W.10.)

'STELAZINE' preparations contain trifluoperazine and are intended for use in the treatment of psychoses, especially schizophrenia, and also in paranoid patients. Administration of the drug is said to have resulted in rapid improvement in the behaviour and emotional state of patients who have proved intractable to other drugs and other forms of treatment. Issued as tablets of 1 and 5 mg. in containers of 50 and 500, and as 1-ml. ampoules containing 1 mg., in packs of 12. (Smith Kline & French Laboratories Ltd., Coldharbour Lane, London, S.E.5.)

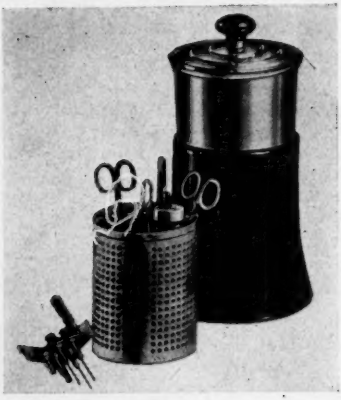
'SYRUP V-CIL-K' is an oral liquid preparation, each 5 ml. of which contains 125 mg. of penicillin V (phenoxymethylpenicillin) as the potassium salt. Issued as dry granules to which water is added at the time of dispensing, in bottles of 30 and 60 ml., each with plastic spoon. (Eli Lilly & Co. Ltd., Basingstoke, Hants.)

'TYROMIST' throat spray contains tyrothricin, 0.02%; cetrimide, 0.05%; and amethocaine hydrochloride, 0.05%. It is said to give 'immediate symptomatic relief and rapid elimination of infection' in cases of acute sore throat. Supplied in plastic atomizers containing 25 ml. (British Schering Ltd., 229-231 Kensington High Street, London, W.8.)

'VALLERGAN' preparations contain trimeprazine tartrate and are intended for the relief of pruritus in dermatological conditions such as chronic urticaria and infantile eczema, and as an oral pre-anæsthetic medication for children. Issued as sugar-coated tablets containing 10 mg., and as a syrup containing 2 mg. in each ml. The syrup is also available in an increased strength ('vallergan forte') containing 6 mg. in each ml., and intended particularly for pre-anæsthetic medication in children. (Pharmaceutical Specialities (May & Baker) Ltd., Dagenham, Essex.)

NEW APPARATUS

'SURQUALET' sterilizers are now available in a new design fitted with a replaceable safety cut-out which comes into operation if the sterilizer



should boil dry. These one-pint sterilizers boil in ten minutes, are portable, and a leatherette carrying case is also available. (Surgical Equipment Supplies Ltd., Westfields Road, North Acton, London, W.3.)

FILM NEWS

Habit Training, *Choosing a Career*, *For Better for Worse*, and *That Time of Life* are sound filmstrips produced by the Central Council for Health Education to promote group discussion on situations which can arise in any family and which affect mental and physical health. Each strip lasts for just under five minutes, is 35 mm. in size, and can be purchased or hired from the Central Council for Health Education, Publications Department, Tavistock House North, Tavistock Square, London, W.C.1.

ROYAL SOCIETY OF MEDICINE

THE next meeting of the Section of General Practice will be held at 8.15 p.m. on Wednesday, January 21, when the subject for discussion will be 'Irregular Uterine Hæmorrhage'.

PRIZES

THE *Brackenbury Prize* for 1960, approximately £100 in value, will be awarded at the discretion of the Council of the British Medical Association for the best contribution on 'The Problem of the Ageing Population' and any member of the B.M.A. is eligible to compete. Entries must be received by January 31, 1960. Full details may be obtained from the Secretary, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1.

FORTHCOMING CONFERENCES

THE *Fifteenth International Tuberculosis Conference* will be held in Istanbul on September 11 to 18, 1959, inclusive, under the chairmanship of Professor Tevfik Saglam (Turkey). Full details may be obtained from the Secretariat of the International Union against Tuberculosis, 15 rue Pomereu, Paris 16e, France.

The Promotion of Health in Middle Age will be the subject for discussion at a seminar for medical officers, to be held at the Ivanhoe Hotel, Bloomsbury Street, London, W.C.1, from February 24 to 27, 1959, inclusive. Full details may be obtained from the Medical Director, Central Council for Health Education, Tavistock House North, Tavistock Square, London, W.C.1.

THE *Sixth Annual Refresher Course in Child and Family Psychiatry* will be held at the Department of Child and Family Psychiatry of the Ipswich and East Suffolk Hospital, 11 Fore Street, Ipswich, from March 16 to 20, 1959, inclusive. Provisional applications for the course, which is recognized by Cambridge University Medical School, under the Ministry of Health postgraduate scheme for general practitioners, should be made immediately to the address given above.

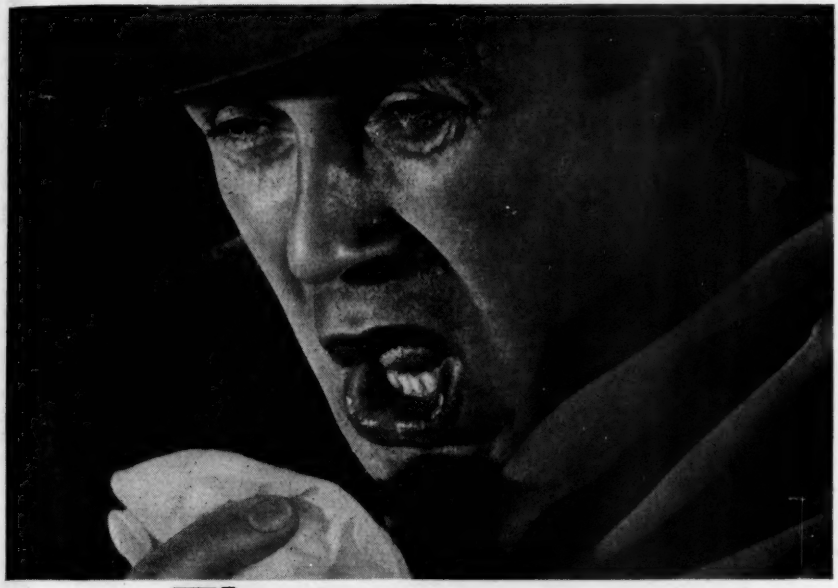
DEATHS IN 1957

THE recently published Part I of 'The Registrar General's Statistical Review of England and Wales for the Year 1957' is able to record several new low records in mortality rates. The infant mortality rate, for instance, at 23 per thousand related live births, is the lowest annual rate ever recorded in England and Wales, whilst the number of deaths from maternal causes (349) was also the lowest ever recorded and means that maternal mortality has declined by nearly 75% since 1945. Deaths from tuberculosis were also down (4,784)—to less than a quarter of what they were in 1949. Deaths from diphtheria (six) and scarlet fever (10) were also record low numbers, whilst the 88 deaths from whooping-cough equalled the record low number of 1955. On the debit side were the two deaths from smallpox—the first in this country since 1953.

G.P's AND HOSPITAL DOCTORS IN SCOTLAND

THE number of doctors of all grades employed in the Scottish hospital service now stands at 2,886, of whom 932 are consultants. This represents an increase of about 30% in the last eight years: consultants and senior hospital medical officers have increased by over 28%,

Something new for coughs



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A single dose of 'Thorpax' produces an almost immediate response and is effective for 3-5 hours. During this period voluntary clearing of the airways remains adequate.

'Thorpax' is well tolerated by patients of all ages and does not cause sedation, respiratory depression, gastric disturbance or constipation.

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senior registrars by 23%, and junior staff by 34%. The main interest of these figures lies in the fact that they mean that in Scotland the profession is now almost equally divided between hospital doctors and general practitioners, the number of the latter being 2,890—2,578 principals and 312 assistants. This is in striking contrast to Western Germany where, of the 68,000 doctors in practice, 29% work in hospitals and 71% in general practice.

THE CHOICE OF POISONS

Of the 860 deaths by suicidal poisoning in England and Wales in 1956, 702 resulted from the taking of 'analgesic and soporific substances', according to figures recently issued by the General Register Office. In the vast majority of cases one of the barbiturates was the lethal drug of choice but aspirin was responsible in 147 cases, and carbromal in seven. Of the remaining 158 cases, cyanide was used in 32 cases, lysol in 24, and Easton's syrup tablets in one. Barbiturates also head the list in deaths by accidental poisoning, accounting for 223 of the 356 deaths in this category. Aspirin comes next (29 cases). Insulin was responsible for three deaths in this category, and methylated spirits for one.

A WARNING

The consequences of not belonging to one of the medical defence societies is well brought out by an episode reported in the annual report of the Liverpool Regional Hospital Board for the year ended March 31, 1958. During the year two cases occurred in which a medical defence society refused to give indemnities under Ministry Circular H.M.(54)32, on the grounds that the doctors concerned were out of benefit. As a result of these two cases the Board has reviewed the conditions of service of the medical staff, and has decided that in future membership of a medical defence society shall be compulsory.

MIGRAINE IN CHILDREN

'Migraine continues to be one of the most prolific causes of diagnostic confusion, anxiety and exasperation', according to Dr. C. C. Harvey, Pædiatrician to the County Council of the West Riding of Yorkshire, in the county medical officer's report for 1957. 'The number of children on my index whose appendixes have been whipped out during an acute migraine attack has now passed a joke. One of these unnecessary appendix operations led to the complication of a serious subphrenic abscess. Mother and two brothers of this child had also had their appendixes removed. The reason here perhaps is that it is not generally recognized how the motor component of migraine may express itself by abdominal colic as well as by vomiting. It was a shock to realise that the mother of one of my migraine children was herself receiving psychiatric electrical treatment for what was evidently an unrecognized prodromal hemiparesis of her own migraine attacks. Several older school children have reported decisive relief by taking compound tablets in the prodromal phase of their attacks, so that their former serious loss of school time has been almost abolished'.

THE PRICE OF PROGRESS

An interesting commentary on the changing face of medicine is provided by the following quotation from the annual report for 1957 of the medical officer of health for Heston and Isleworth: 'There has been no smallpox in the borough since 1930, no death from whooping cough since 1947, and no case of diphtheria since 1950, so propaganda to prevent parents acquiring a false sense of security is difficult'.

A PUBLIC HEALTH CATASTROPHE

Details of what is described as an outbreak of food poisoning which 'has perhaps no parallel in modern public health history' are given by C. O. Karunakaran (*J. Indian med. Ass.*, 1958, **31**, 204). The outbreak involved 828 cases, with 106 deaths. The cause of it was contamination of food by the organic phosphorus insecticide known as compound E605, or 'folidol'. This occurred on board a ship which arrived in Cochin on April 1, with 55 carboys, each containing 3 gallons of 'folidol', 15 of which were defective. The leakage was noted on unloading but, apart from a survey by insurance agents to assess the loss, no further action was taken and contaminated bags of foodstuff were distributed throughout Travancore. The first cases occurred on April 13 and further cases occurred until May 3.

SKIING AND LONGEVITY

Finnish champion skiers have significantly lower serum cholesterol levels than the rest of the population, according to M. J. Karvonen *et al.* (*Ann. Med. exp. Fenn.*, 1958, **47**, 75). Among 44 male champions the mean was 204 mg. %, compared with 229 mg. % for males of the same age-group. The comparable figure for 15 female champions was 199 mg. %, compared with 226 mg. % for females of the same age-group. The serum cholesterol levels of the skiers did not rise significantly with age, whereas all but one of the male control group showed such a rise. Although no definite conclusions are drawn from these findings, it is

noted that the life expectation of Finnish skiers exceeds that of the general male population by several years, and it is suggested that a low serum cholesterol level may be one of the factors increasing the longevity of skiers.

GERMAN SPAS

Health Resorts in Germany and *Climatic Cures in Germany* give details of the curative facilities available at German spas and health resorts. Available from the German Tourist Information Bureau, 6 Vigo Street, London, W.1, or the Association of German Spas, Lotharstrasse 19, Bonn.

PUBLICATIONS

Handbook of Respiration, compiled by P. L. Altman, J. F. Gibson, and C. C. Wang, is the sixth of the series of publications being prepared under the direction of the Division of Biology and Agriculture, National Academy of Sciences and National Research Council. Like its predecessors, it presents the information in tabular form, and constitutes a valuable work of reference—particularly for research workers. (W. B. Saunders Co. Ltd., price 52*s.* 6*d.*)

Rheumatism, by Oswald Savage, O.B.E., F.R.C.P., is a *Family Doctor* booklet which has been written to help people with rheumatism and people who may fear its onset. (Price 1*s.*)

The Care of the Elderly is a report of the ninth conference of the National Old People's Welfare Council held in London in April 1958. (26 Bedford Square, London, W.C.1, price 3*s.* 6*d.*)

Publications of the World Health Organization, 1947-1957: A Bibliography.—This volume contains a complete list of everything published by the World Health Organization between 1947 and 1957. (H.M. Stationery Office, price 17*s.* 6*d.*)

The Pasteur Fermentation Centennial 1857-1957 is a record of a scientific symposium held in New York on the occasion of the 100th anniversary of the publication of Louis Pasteur's 'Mémoire sur la Fermentation Appelée Lactique'. (Chas. Pfizer & Co. Inc., New York.)

A Doctor in Parliament, by Donald McI. Johnson, M.P., M.B., B.CH.—Those who have read his earlier books will not need to be told that this book is very much about Dr. Donald Johnson in Parliament. The grammar in places is appalling, the sentences long and meandering, the book a disjointed mosaic, though it improves towards the end. This is a pity, for Dr. Johnson has good points to make about Parliamentary procedure, personal liberty, the National Health Service, mental health and certification, as well as the inside story of the way he has helped to bring these matters before the public for its benefit. His zeal and pertinacity are obvious; but less haste, less egotism and more care in revision would have made it easier for his readers to appreciate his work and the tale he has to tell. (Christopher Johnson Publishers Ltd., price 18*s.*)

Surgeon At Arms, by Daniel Paul with John St. John, consists of the reminiscences of one of the surgeons in the First Airborne Division who was dropped by parachute at Arnhem and soon thereafter taken prisoner. There has perhaps been a surfeit of war reminiscences recently, but this one will appeal to all who were at Arnhem or who were members of any of the airborne divisions. It pays a well-earned tribute to the work of the Dutch resistance movement. (Heinemann, price 16*s.*)

OFFICIAL PUBLICATIONS

Report of the Ministry of Health for the Year 1957. Part II. On the State of the Public Health.—One of the sombre features of this report of the chief medical officer of the Ministry of Health is the increased incidence of fatal complications of vaccination against smallpox; three fatal cases of generalized vaccinia and six cases of encephalitis following vaccination, two of which proved fatal. Two of the fatalities from generalized vaccinia occurred in children with agammaglobulinæmia, and the third in a child with eczema. One of the fatal cases of encephalitis occurred in a man, aged 49 years, who was revaccinated after a primary vaccination done in infancy.

The other sombre feature of the report is the further steep rise in the number of new cases of gonorrhœa: 24,381, compared with 20,388 in 1956 and 18,064 in 1951. As the report points out, 'it is now apparent that penicillin, effective though it has been, cannot by itself make a lasting impression on the incidence of this disease'. (H.M. Stationery Office, price 13*s.*)

Rehabilitation and Resettlement of Disabled Persons is the third report of the Standing Committee of the Ministry of Labour and National Service responsible for coordinating the work of the various government departments concerned in this field. (H.M. Stationery Office, price 1*s.* 3*d.*)

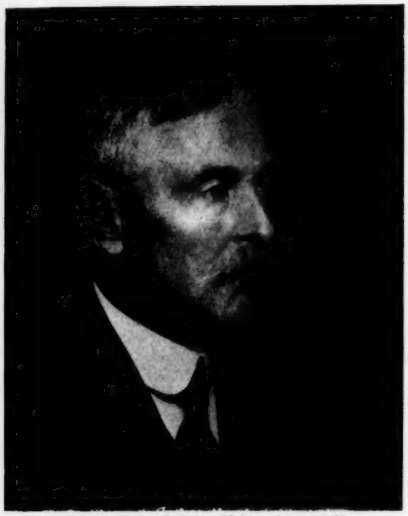
THE PRACTITIONER

Fifty Years Ago

'Fever, the eternal reproach to the physicians'.—Milton: *Reason of Church Government: Preface.*

JANUARY 1909

THIS number, according to 'Notes by the Way', 'forms a complete account of almost every aspect of two of the most important diseases to which mankind—and especially children—are susceptible in this country. The reason for their importance is different in the two cases. Scarlatina has a comparatively low mortality, and is in most cases a mild disease; yet it is widespread, and exacts a heavy toll on the rising generation. Diphtheria, on the other hand, is—or was, previously to the discovery of anti-toxin—a malady of most formidable character; and, though less prevalent than scarlet fever, was a greater enemy to the race owing to its high mortality and the terrible distress which it caused. The two diseases have much in common, and it is appropriate that they should be considered side by side. There is, however, one important difference . . . Diphtheria has yielded the secret of its causation to modern research . . . But in the case of scarlet fever all is in confusion. It is true that a strong case has been made out in favour of a streptococcus of peculiar characters . . . but still serious difficulties remain, and probably the majority of bacteriologists regard this organism as a secondary infection'.



E. W. Goodall, O.B.E., M.D. (1861-1938)

The opening article, 'The Complications of Scarlet Fever', is from the pen of William Hunter, M.D., F.R.C.P., F.R.S.Ed., Physician to the London Fever Hospital, and to Charing Cross Hospital. Sir John F. H. Broadbent, Bt., M.D., F.R.C.P., Assistant Physician to the London Fever Hospital, and Physician to Outpatients, St. Mary's Hospital, deals with 'The Heart in Scarlet Fever and Diphtheria'. Nestor Tirard, M.D., F.R.C.P., Physician to King's College Hospital, and Professor of Medicine in King's College, London, discusses 'The Renal Complications of Scarlet Fever and Diphtheria'; J. Herbert Parsons, D.Sc., F.R.C.S., Assistant Ophthalmic Surgeon, University College Hospital, describes 'Ocular Complications', whilst Macleod Yearsley, F.R.C.S., Senior Surgeon to the Royal Ear Hospital, writes on 'The Ear Complications'.

E. W. Goodall, M.D., Medical Superintendent of the Eastern Hospital, Homerton, begins his article 'On the Diagnosis of Scarlet Fever and Diphtheria': 'An idea of the amount and variety of error made in the diagnosis of these diseases in London, can be obtained by a reference to the statistics published by the Metropolitan Asylums' Board. In the year 1907, of 24,434 cases, sent to the fever hospitals with the diagnosis of scarlet, 1,670, or 6.8 per cent., turned out to be some other disease . . . Of 6,924 cases certified to be diphtheria, 1,180, or 17.0 per cent., were found to be some other disease. That all this error is avoidable cannot be maintained; but some of it is; and this I believe to be quite an appreciable part'.

Edward Wilberforce Goodall (1861-1938) was described at the time of his death as 'the Murchison of our age . . ., almost of the rank of Budd' (Major Greenwood). The whole of his professional life was spent in the study of infectious diseases. As superintendent of two London Fever hospitals—the Eastern at Homerton and the North Western at Hampstead—his vast clinical experience and his extensive knowledge of the literature made his professional opinion unrivalled. At the Royal Society of Medicine he was President of the Epidemiological and Historical Sections.

Arthur Whitfield, M.D., F.R.C.P., Professor of Dermatology in King's College, in his paper 'The Differential Diagnosis between the Rashes of Scarlatina, Diphtheria, and other Skin Eruptions', writes: 'The question of erythematous rashes in diphtheria has become some-

what more complicated by the introduction of the antitoxic serum, which is itself capable of giving rise to an erythematous eruption. I have, however, seen a few instances of scarlatiniform eruption in cases of diphtheria in which the antitoxin had not been administered'.

Describing 'Treatment of Diphtheria', Claude B. Ker, M.D., F.R.C.P., Medical Superintendent of the Edinburgh City Hospital, confesses: 'Fifteen years ago the treatment of diphtheria was practically ineffective. When we look back upon the methods usually employed at that time, we are sometimes inclined to wonder if the remedies in vogue did not actually increase rather than diminish the mortality of the disease'. J. D. Rolleston, M.D., Assistant Medical Officer, Grove Fever Hospital, contributes an article on 'Diphtheritic Paralysis', based on a study of 1,500 cases of diphtheria in the course of six years.

'Is scarlet fever primarily due to streptococcal infection, or do these micro-organisms only represent a subordinate or secondary infection, the micro-organism primarily responsible for the disease being still unknown?' asks M. H. Gordon, M.D., B.Sc., late Assistant Bacteriologist to the Royal Commission on Sewage Disposal, in his paper 'The Bacteriology of Scarlet Fever'. He submits evidence pointing to two different streptococci being concerned: one corresponding with Klein's *S. scarlatinæ*, the other indistinguishable, morphologically or culturally, from *S. pyogenes*.

The remaining articles are entitled 'The Bacteriology of Diphtheria', 'Antistreptococcic Serum in Scarlet Fever and Diphtheria', and 'Scarlet Fever and Diphtheria from the Public Health Point of View'.

'Notes from Foreign Journals' are exclusively devoted to these two diseases. Some of the items are of historic interest only. According to the *Deutsche Medizinische Wochenschrift*, pyocyanase *in vitro* inhibits the growth of *B. diphtheriæ* and in comparatively small quantities kills large quantities of these bacilli. 'In actual treatment of the disease with this substance, the throat of the patient is sprayed three times a day . . . with 2 c.c. of pyocyanase warmed to 40°C. It appears to bring about the disappearance of the membrane, and favourably to promote the general condition of the patient. The fœtor from the mouth is quickly stopped. Pyocyanase should only be used in conjunction with the antitoxin treatment. The clinical experiences already obtained demand further investigations in the matter'. According to another observation, however, quoted by the same journal, in very severe cases of septic diphtheria pyocyanase 'appears to be of no effect. It does not inhibit the persistence of the bacillus diphtheriæ, nor does it destroy the bacilli in cases of extra-persistency, and of chronic diphtheria'. W. R. B.

The
Ernest and Minnie Dawson Cancer Trust

A COMPETITION FOR GENERAL MEDICAL PRACTITIONERS

The purpose of the Ernest and Minnie Dawson Cancer Trust, which came into being in 1955, is to arrange competitions between selected general medical practitioners, and to give big financial prizes to such practitioners who from time to time make what is considered to be the most valuable contribution to the early diagnosis, prevention and treatment of cancer and to knowledge of its causes.

The second competition, which will close on the 1st May, 1959, will take the form of a thesis on cancer. The subject matter is at the discretion of the entrant, and may relate to cancer in various sites or cancer of one organ; it must also lay emphasis on one or more of the following: (*a*) early diagnosis; (*b*) causes; (*c*) prevention, and (*d*) treatment. All entries must contain original thought and observation, and be the result of personal endeavour.

The competition is open to doctors mainly engaged in general practice who practise and/or reside in Lancashire or Yorkshire; and the maximum prizes offered are £1,500 (first) and £500 (second), subject to the merit of the entries submitted.

Entry forms and detailed conditions of entry may be obtained from the Clerk to the Trust, The Ernest and Minnie Dawson Cancer Trust, 89a Fishergate Hill, Preston, Lancs.

E. PEARSON,
Clerk to the Trust.

The Medical Service of the Royal Navy

VACANCIES FOR MEDICAL OFFICERS

Candidates are invited, for Short Service Commissions of 3 years, on termination of which a gratuity of £600 (tax free) is payable. Ample opportunity is granted for transfer to Permanent Commissions on completion of one year's total service. Officers so transferred are paid instead a grant of £1,500 (taxable).

All entrants are required to be British subjects whose Parents are British subjects, medically qualified, physically fit, and to pass an interview.

Full particulars from:
THE ADMIRALTY MEDICAL DEPARTMENT,
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